EXPLORING THE FRACTIONATION OF AUTISM SPECTRUM DISORDER AT THE COGNITIVE LEVEL

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Abstract

The behavioural symptoms of autism spectrum disorder (ASD) are thought to reflect underlying cognitive deficits/differences. Single cognitive deficit models of ASD have attempted to reduce the varied behavioural symptoms of the disorder to a single underlying cognitive deficit. However, there is a need to move on from these single cognitive deficit accounts of ASD. Therefore, the main focus of the thesis is to explore the potential for a multiple cognitive model of ASD using the predictions of the fractionated triad account.

The data that is examined in the thesis originated from the Twins Early Development Study (TEDS) where one or both children met diagnostic criteria for ASD. A subsample of adolescents took part in the Social Relationship (SR) study. Overall, 181 adolescents with a diagnosis of ASD and 73 unaffected co-twins were included in the SR sample, plus an additional 160 comparison control participants.

The findings in this thesis do not support a strong version of the fractionated account of ASD, in which distinct causes at the genetic and neural levels relate to distinct deficits at the cognitive level, and are associated with distinct symptoms of ASD at the behavioural level. There were some selective relationships between cognitive atypicalities and the behavioural symptoms of ASD, but these differed depending on the diagnostic symptom measure used. A weaker version of the fractionated theory is supported in which multiple cognitive deficits characterise ASD, and these cognitive deficits relate to distinct symptoms, as in the strong version, but a single cognitive deficit can explain more than one symptom domain, and more than one cognitive deficit can explain a single symptom domain. General interpretations are discussed using the framework of the fractionated triad theory of ASD. The limitations of the current thesis and potential future research are also considered.

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Chapter 1 An Introduction to Autism Spectrum Disorder

This chapter sets the scene for the empirical work presented in this thesis by reviewing the literature on autism spectrum disorder to provide an overview of the history of the disorder, how it is currently classified, and the causes of the disorder at the genetic, neural, and cognitive levels.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is classically described in terms of social-communication impairments and restricted and repetitive behaviours. ASD is currently diagnosed behaviourally. The prevalence of ASD is estimated to be around 1.2% in the UK (Baird et al., 2006), but differs somewhat according to country (see Elsabbagh et al., 2012, for a systematic review of epidemiological surveys). The reported prevalence of ASD has increased over the last few decades, most likely due to increased awareness by clinicians and families, improved detection and the broadening of diagnostic criteria to encompass a wider range of individuals.

1.1 History

The term ‘autism’ was originally coined by Bleuler (1911) to describe a secondary symptom of schizophrenia. ‘Infantile’ autism was first described by Kanner in 1943. He noted a group of 11 children who all displayed similar behaviours, such as the inability to relate to themselves, profound aloneness, lack of social communication, isolated special abilities, delayed echolalia, literalness, sensory issues, insistence on sameness, repetitive behaviours, and no interest in people. Kanner (1943) clustered these core symptoms into a distinct disorder termed ‘infantile autism’, instead of previous descriptions of these children as ‘feebleminded’ or schizophrenic. Coincidentally, Asperger (1944) also used the term ‘autism’ to describe children with “severe and characteristic difficulties in social integration” (p. 37, Frith, 1991). To add to Kanner’s description of autism, Asperger also highlighted the lack of facial and gestural expressions and abnormal eye gaze in this disorder. He also considered autism as a lifelong condition that persists into adulthood.

For the next 30 years, autism was widely regarded as a form of ‘childhood schizophrenia’ caused by a lack of maternal warmth (Kanner, 1949) or “emotional refrigeration” (Eisenberg &

Kanner, 1956). This became known as the 'refrigerator mother' hypothesis, which was advocated by psychologists such as Bettelheim (1967). This theory shaped the understanding of autism in the scientific and general population during the 1960s, but the theory is widely discarded today.

The 1970s were marked by major advancements in the understanding of the aetiology of autism with the first studies to show that autism and schizophrenia were distinct (DeMyer, Churchil, Pontius, & Gilkey, 1971; Kolvin, 1971; Rutter, 1972, 1974), the first clinical definitions of autism (Rutter, 1978), the first genetic studies of autism (Folstein & Rutter, 1977; Rutter, 2000) and the introduction of the concept of the 'autistic spectrum' and the 'triad of impairments' (Wing & Gould, 1979). Wing and Gould (1979) introduced the concept of the 'triad of impairments' in their pioneering study after finding that all of the children in their study with impairments in social interaction also exhibited repetitive stereotyped play and also often had impairments in verbal and nonverbal communication. It was concluded that the autism spectrum consists of a 'triad of impairments' in social interaction, communication and imagination, with varying severity at the individual level. It was not until 1980 that autism was diagnostically defined as distinct from schizophrenia, with separate diagnostic criteria for autism in the Diagnostic and Statistical Manual third edition (DSM III) (American Psychiatric Association, 1980).

1.2 Diagnosis & Symptomatology

Until recently, clinicians have used the Diagnostic Statistical Manual version IV-text revised (DSM-IV-TR) (American Psychiatric Association, 2000) or the International Classification of Diseases version 10 (ICD-10) (World Health Organisation, 1992) criteria, which categorised individuals with ASD under the umbrella term of pervasive developmental disorders (PDD). Using the DSM-IV-TR, clinicians could diagnose individuals with Autistic Disorder, Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS), Asperger's Disorder, Rett's Disorder, or Childhood Disintegrative Disorder. A diagnosis depended upon the presence of a 'triad of impairments' in social interaction, communication and repetitive and restricted behaviours and interests.

The DSM-5 was introduced in May 2013, and 'autism spectrum disorder' replaced the term 'pervasive developmental disorders', with the individual diagnoses of Asperger's and PDD-NOS

being removed (American Psychiatric Association, 2013). The new term was preferable to families and clinicians, with the exception of the preference for the diagnosis of Asperger's syndrome for individuals with ASD symptoms but with intelligence and cognitive ability in the 'gifted' or typical range. Many self-advocates and families identified with this term viewing it as less stigmatising and more descriptive of a more subtle form of ASD. The absence of a formal category for Asperger's disorder/syndrome has prompted concern for many individuals, but Lord and Jones (2012) pointed out that the new criteria eliminate the confusion around the distinction between Asperger's Disorder, PDD-NOS, and autism.

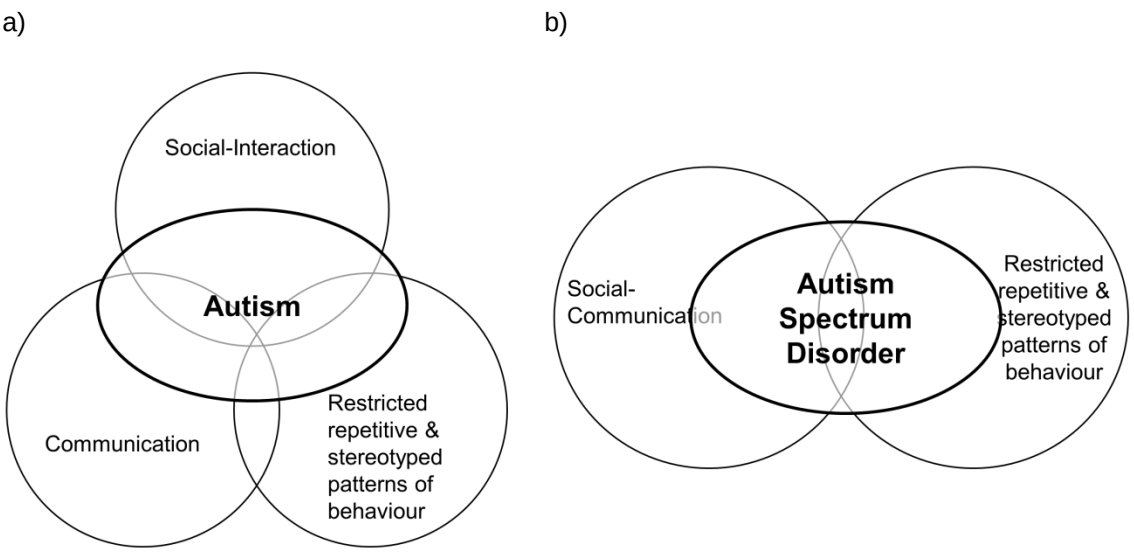


Figure 1.1. a) DSM-IV classification for Pervasive Developmental Disorders; b) DSM-5 classification for Autism Spectrum Disorder.

The DSM-5 diagnostic criteria for ASD are presented schematically in Figure 1.1. ASD is defined as a dyad of impairments, as compared to the triad of impairments in the previous version, with social and communication symptoms collapsed into one symptom domain. The decision to collapse social and communication symptoms into one domain was based on substantial literature, such as factor analytic studies showing one social-communication factor (Gotham, Risi, Pickles, & Lord, 2007). According to the DSM-5, a diagnosis of ASD depends upon the presence of: 1) persistent deficits in social-communication and social-interaction, and: 2) restricted, repetitive patterns of behaviour, interests, or activities. ASD can be diagnosed with accompanying intellectual and/or language impairment, listed under 'specifiers'. In addition,

individuals who have deficits in social communication, but do not meet criteria for ASD, may be evaluated for 'social communication disorder' in DSM-5.

ASD is rarely diagnosed before a child is three years old, with the average age of diagnosis at four years old. The age at diagnosis can depend on the number of behavioural symptoms identified, with children exhibiting more symptoms receiving an earlier diagnosis (Maenner et al., 2013). As infants rarely receive a diagnosis before two years old, studies investigating the emergence of autism-like behaviours in the first two years of life have focused on infants genetically at risk of ASD (younger siblings of children with an ASD diagnosis; Elsabbagh & Johnson, 2010). Findings from these 'infant sib' studies suggest that little that is different in the behaviours before age six months, with a decline in social-communication skills by 12 months of age in many infants later diagnosed with ASD (Ozonoff et al., 2010). Due to the reduction in family stress and earlier intervention that an earlier diagnosis can provide, a clinical screening tool for early detection of ASD in toddlers has been investigated and developed (Baron-Cohen et al., 2000).

1.2.1 Social-Communication Symptoms

Social deficits have been emphasised as the most universal and specific characteristics of ASD (Volkmar, State, & Klin, 2009). The DSM-5 proposes three criteria in defining social deficits: 1) social-emotional reciprocity, 2) non-verbal communicative behaviours, and 3) deficits in developing, maintaining and understanding relationships.

The social-emotional reciprocity impairments include absence of sharing interests, lack of initiation and maintaining conversation, no turn taking, absence in sharing affect, and lack of initiation or social approach. In early childhood, young children with ASD may show an inability to share and direct attention towards others, have difficulty imitating others and may not recognise others' emotions (Happé, 1994b). Some children may ignore even a familiar person, and show an apparent lack of social interest. Furthermore, children with ASD do not appear to initiate joint attention with another person (e.g., Naber et al., 2008); parents of infants with ASD report that their toddler did not offer, give, show, or point to objects in relation to someone else (Wimpory, Hobson, Williams, & Nash, 2000).

The nonverbal communication deficits are characterised by poor verbal and nonverbal communication skills in social contexts (see Prelock & Nelson, 2012, for a review). These deficits are apparent in infancy, for example, infants with ASD avoid eye contact, do not greet, and fail to wave to their parents (Wimpory, et al., 2000). Abnormal eye contact has been reported in ASD ever since Kanner's (1943) first descriptions of the disorder, with studies suggesting that this abnormality is in the use of eye contact, and is not merely due to avoidance of people (Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995). There appears to be a delay in the development of gesture production in ASD (Charman, Drew, Baird, & Baird, 2003), and in adolescence gestures are less synchronised with speech (de Marchena & Eigsti, 2010). In addition, children with ASD produce unique and unusual facial expressions (Yirmiya, Kasari, Sigman, & Mundy, 1989), and less natural and more awkward facial expressions (Grossman, Edelson, & Tager-Flusberg, 2013).

Deficits in relationships are characterised by the lack of imaginative play with peers, and also a disinterest in people and making friends. Individuals with ASD may not adjust their behaviour to suit different social contexts, for example indiscriminately approaching strangers. From a young age, children with autism may have no age-appropriate friends, with many forming bonds with adults instead (Hauck, Fein, Waterhouse, & Feinstein, 1995). Individuals may have difficulties forming and maintaining relationships, with individuals with ASD reporting greater loneliness and less satisfaction with their friendships (Bauminger & Kasari, 2000) and an increased prevalence of bullying (van Roekel, Scholte, & Didden, 2010). Social-interaction impairments persist into adulthood (Happé & Charlton, 2012) and even the most socially capable adults with ASD still show social-interaction impairments.

1.2.2 Restricted and Repetitive Behaviours and Interests

Restricted and repetitive behaviours and interests (RRBIs) are a core symptom of ASD (for a comprehensive review, see Leekam, Prior, & Uljarevic, 2011). This is perhaps the least researched symptom domain of ASD. The DSM-5 proposes four criteria in defining RRBIs: 1) stereotyped or repetitive motor movements, 2) insistence on sameness, 3) highly restricted and fixated interests, and 4) hyper- or hypo-reactivity to sensory input or unusual sensory interests.

Stereotyped or repetitive motor movements are shown by most children with ASD at some stage in their development, either using their own body parts, such as hand flapping and

rocking, or using other objects, such as spinning wheels and the repetitive lining up of toys. Echolalia is present in some children with autism, in which words or phrases from other people or sources are repeated immediately or with delay. Idiosyncratic speech is also characteristic of ASD. These behaviours are generally seen in younger children with ASD, or those who are more developmentally delayed (Leekam, et al., 2011).

The restricted and repetitive behaviours in ASD may also present as insistence that aspects of the environment stay the same, inflexible adherence to routines and persistence on certain foods (Leekam, et al., 2011). Individuals with ASD become extremely distressed at small changes in their environment or daily routines. ASD can be characterised by concreteness and rigidity of thinking (Grandin, 1995). Most individuals with ASD restrict food acceptances (72%) or refuse most food items (57%), which are commonly related to food presentation (49%) (Schreck & Williams, 2006).

In addition, highly restricted, fixated interests that are abnormal in intensity or focus are characteristic of ASD. Individuals with ASD may show an intense interest in a particular object, topic or activity that is obsessive and sometimes to the exclusion of all other activities. Gathering facts and information through verbal learning and rote memory on special interests is common (Klin, Danovitch, Merz, & Volkmar, 2007). Klin et al. (2007) also noted over 250 exemplars of special interests, from typical topics such as dinosaurs and Power Rangers, to specialised topics such as tsunamis and astronomy, to idiosyncratic topics such as cul-de-sacs and deep-fat fryers. It was also noted that the way special interests are pursued and the content learned is atypical in ASD.

Lastly, sensory abnormalities are apparent in ASD, and have been included in the diagnostic criteria for the first time in the latest version of the DSM. Sensory abnormalities can manifest as either an over- or under-reactivity to sensory input or in unusual interests in sensory aspects of the environment. Sensory abnormalities have been found to be very common in children with ASD (Klintwall et al., 2011). The most common sensory abnormalities were found to be over-reactivity to sound (44%) and under-reactivity to pain (40%). Other examples of sensory abnormalities were under-reactivity to temperature, over-reactivity to touch, abnormal reactions to visual stimuli, and oversensitivity to smell.

1.2.3 Symptom Severity

The autism behavioural phenotype can be seen as the severe end of a set of continuous, quantitative traits that merge with the general population. Additionally, within the diagnosis of ASD, the degree of impairment can differ, from mild to severe. For example, there is considerable variability in the social-interaction impairments that individuals with ASD exhibit; from complete isolation and no apparent interest in interaction with others, through to those proficient in friendships who show only subtle impairments in social skills compared to a typically developing individual. Therefore, there is a vast range of severity within ASD making individuals with ASD unique, which led to the often-used quote 'If you know one person with autism then you know one person with autism'.

Severity levels were included in the DSM-5 for the first time. The revisions were implemented to provide information on the presence and severity of symptoms. The addition of a dimensional assessment reflects the wide held opinion that the symptoms of ASD represent a continuum from mild to severe instead of being discrete disorders. In the DSM-5, three severity classifications are used to indicate the degree of impairment for each symptom domain of ASD, from mild which 'require support' through to severe which 'require substantial support'.

Weitlauf, Gotham, Vehorn, and Warren (2014) investigated the validity of the new severity categorisation in ASD diagnoses, finding discrepancies in the distribution of severity categorisations across adaptive and cognitive functioning and autism symptomatology. It therefore remains unclear how clinicians will differentiate the severity levels, with no current quantitative methods or recommendations in use.

1.3 Broader Autism Phenotype

In Kanner's (1943) description of 'infantile autism', he noted that the parents and grandparents of the children shared some features, such as abstract thinking, and limited social interests. The broader autism phenotype therefore refers to the milder autism-like features in the relatives of individuals with ASD, and has been extensively reviewed (see Bailey, Palferman, Heavey, & Le Couteur, 1998; Dawson et al., 2002; Piven, 1999; Sucksmith, Roth, & Hoekstra, 2011).

The notion of a broader autism phenotype was developed from the findings that the risk of reoccurrence of autism in a family was 8.6%, which is 215 times greater than the risk in the general population (Ritvo et al., 1989). Bolton et al. (1994) found that if a child had autism or ASD, then their siblings had an increased chance of having autism or ASD and between 12.4% and 20.4% of the siblings also displayed autistic-like behaviours. In a more recent and comprehensive study, ASD in one child also occurred in a sibling in 10.9% of families (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010).

This led Piven, Palmer, Jacobi, Childress, and Arndt (1997) to investigate the broader autism phenotype in multiplex autism families (families with more than one child with autism) and found that parents, grandparents, and aunts/uncles of the autism probands all showed milder autism-like behaviours (social-communication deficits and stereotyped behaviours), which were qualitatively similar to the defining characteristics of autism. In addition, several studies have noted features in relatives of autism probands that are milder but similar to features associated with ASD, for example, language deficits (e.g., Taylor et al., 2013), personality characteristics (e.g., Piven et al., 1997) and cognitive and emotional deficits (e.g., Briskman, Happe, & Frith, 2001; Happé, Briskman, & Frith, 2001; Szatmari et al., 2008; Tajmirriyahi, Nejati, Pouretemad, & Sepehr, 2013) leading to the development of measures to assess the broader autism phenotype (Dawson et al., 2007; Hurley, Losh, Parlier, Reznick, & Piven, 2007). Another interesting finding is that fathers of children with ASD are over-represented in professions such as physics, engineering, computer science, and mathematics (Baron-Cohen et al., 1998).

Other studies have investigated the broader autism phenotype in unaffected siblings of those with an ASD. Constantino, et al. (2010) reported increased subclinical autistic traits in siblings of autism probands from multiplex families compared to a relative absence of autistic traits in siblings from single-incidence families. In addition, Sucksmith, et al. (2011) reviewed the existing research findings and found that the emerging broader autism phenotype in younger infant siblings of autism probands could be defined by language delay and social deficits, such as abnormal gaze patterns, lack of requesting behaviours, poor initiation and responding to joint attention, and problems disengaging from visual stimuli. In older siblings of autism probands, the broader autism phenotype was defined by behavioural problems (pragmatic language skills, social responsiveness, and reciprocal social interaction), cognitive deficits (mentalising, emotion recognition and face-processing problems, executive dysfunction, and a local processing bias),

elevated personality traits (aloof, rigid and hypersensitive) and psychiatric disorders (such as anxiety and depression).

Furthermore, there is evidence for the intergenerational transmission of autistic-like traits in the general population (Constantino & Todd, 2005). The study reported modest correlations between social impairments in parents and their children, indicating transmission of subclinical autistic traits across generations in the general population. In addition, parental pairs of children with ASD were most commonly characterised by a single parent out of the parental pair with the broader autism phenotype (Sasson, Lam, Parlier, Daniels, & Piven, 2013) and the broader autism symptomatology in parents has been associated with their child's ASD symptomatology (Maxwell, Parish-Morris, Hsin, Bush, & Schultz, 2013).

1.4 Psychiatric Comorbidity

High rates of comorbidity with other psychiatric conditions have been reported in ASD (Leyfer et al., 2006; Mazzone, Ruta, & Reale, 2012; Simonoff et al., 2008). Simonoff, et al. (2008) conducted the first systematic study of associated psychiatric disorders in ASD using an epidemiological, population-representative sample. Overall, 71% of children with ASD met criteria for at least one current psychiatric disorder. Forty-two percent of children with ASD met criteria for an anxiety disorder, 30% met criteria for an oppositional or conduct disorder, 28% met criteria for attention-deficit/hyperactivity disorder (ADHD) and 1.4% met criteria for a depressive disorder. Autism severity, nor IQ, was a predictor of comorbid psychiatric disorders.

Several psychiatric disorders, such as bipolar and schizophrenia are relatively rare in children, and so rates of comorbidity with ASD are unreported (e.g., Simonoff, et al., 2008). In addition, studies in adults in ASD are limited, but those to date also suggest that adults with ASD suffer from a higher burden of additional psychiatric disorders (Joshi et al., 2013). Lugnegard, Hallerback, and Gillberg (2011) reported that in young adults with Asperger's Syndrome, 70% had experienced at least one episode of major depression, with 50% reporting recurrent depressive episodes, and 50% reporting anxiety disorders. Psychotic disorders, such as bipolar disorder, and substance-abuse disorders were uncommon, as compared to higher rates reported by Hofvander et al. (2009). One of the outstanding questions is whether these

psychiatric symptoms are phenotypic manifestations of ASD or if they are an expression of a separate, but comorbid disorder (Mazzone, et al., 2012).

1.5 Gender Bias

Kanner (1943) originally reported that four times as many males had autism than females, which has consistently been reported since with a male to female ratio of 4:1 (Ehlers & Gillberg, 1993) and 3.3:1 (Baird, et al., 2006), dependent on the criteria used. The ratio is considerably higher towards the more able end of the ASD spectrum, with a male to female ratio of 15:1 (Wing, 1981). The male to female ratio decreases to 2:1 in those with additional learning difficulties.

The specific drivers for the higher prevalence of ASD in males remain unclear. There may be a difficulty in diagnosing ASD in females, perhaps due to its masking by or misdiagnosis as another condition (e.g. eating disorders), females being better able to adapt/compensate, or the inability of current diagnostic measures to detect a more subtle or unusual symptom presentation in females (Dworzynski, Ronald, Bolton, & Happe, 2012). Biological reasons for the gender bias in ASD have also been proposed; specifically the foetal testosterone theory, the X- and Y- chromosome theories and the reduced autosomal penetrance theory (see Baron-Cohen et al., 2011, for a detailed review).

1.6 Aetiology

ASD has a strong genetic basis. Kanner (1943) first hypothesised a biological basis for autism, but this was not considered further until a seminal twin study by Folstein and Rutter in 1977. On the basis of their results, ASD became widely considered as a heritable disorder. Consequently, molecular research began to attempt to discover the genes behind ASD.

1.6.1 Genetic

1.6.1.1 Quantitative genetics

There is compelling evidence from twin studies that ASD has a large genetic component. The psychogenic view of the cause of autism changed when four influential twin studies revealed that the concordance rate for autism was far higher in monozygotic (MZ) twins than for dizygotic

(DZ) twins (Bailey et al., 1995; Folstein & Rutter, 1977; Ritvo, Freeman, Masonbrothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989). Folstein and Rutter (1977) conducted the first twin study comparing the concordance rates of strictly diagnosed autism in twin pairs and found that 36% of MZ twins were concordant for autism compared with no concordant DZ twins for autism. This twin study was the first to determine the significance of genetic factors in the aetiology of autism. Bailey, et al. (1995) subsequently replicated these results in a larger sample and found that the concordance rate for autism in MZ twins was even higher; 69% for MZ twins compared to 0% for DZ twins, which increased to 88% in MZ twins when a broadly defined definition of autism was used. Using twin modelling, the heritability of autism was estimated at 93%.

More recent twin studies of ASD have found a concordance rate of between 88% and 95% for MZ twins and 31% for DZ twins (Rosenberg et al., 2009; Taniai, Nishiyama, Miyachi, Imaeda, & Sumi, 2008). Furthermore, the largest representative twin study of ASD found that genetic factors accounted for 80% of the liability for ASD (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010). In addition, a recent twin study combined a continuous trait approach and diagnostic classification of ASD to provide heritability estimates of 56 to 95% (Colvert et al., 2015). Overall, most twin studies have estimated a high heritability of ASD and have added considerably to our knowledge about the cause of ASD.

In contrast, one twin study has suggested that ASD is only moderately heritable and that ASD is largely due to the shared twin environment (Hallmayer et al., 2011). The study claims that it is the largest and most rigorous twin study to date and included all twin pairs born in California between 1987 and 2004 with at least one twin diagnosed with ASD. It was determined that the heritability of autism was 37% and ASD was 38% with the shared environment accounting for 55% of the liability for autism and 58% for ASD. These estimates are substantially lower than previous twin studies and suggest that autism and ASD are not as heritable as previously proposed. However, the authors did acknowledge that their calculations were subject to a wide margin of error as the sample showed high attrition and consisted of only 192 twin pairs.

It has been proposed that autistic traits, i.e. social and communicative impairments and RRBIs, are continually distributed in the general population with individuals with ASD at the extreme end of the distribution (Hoekstra, Bartels, Verweij, & Boomsma, 2007; Piven, Palmer, Jacobi, et al., 1997; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002). To investigate this notion,

population-based twin studies have investigated autistic traits in the general population (Constantino & Todd, 2005; Constantino, et al., 2010; Edelson & Saudino, 2009; Hoekstra, et al., 2007; Skuse, Mandy, & Scourfield, 2005; Stilp, Gernsbacher, Schweigert, Arneson, & Goldsmith, 2010). Hoekstra, et al. (2007) found that autistic traits show considerable heritability in the general population (57%). Constantino, Hudziak, and Todd (2000) examined the genetic structure of social behaviour in a population-based twin study of autistic traits. The genetic influence of social behaviour was estimated to be 76% which suggests that social impairments are highly heritable. Furthermore, Skuse, et al. (2005) measured social and communicative impairments in a population-based twin study and found that the genetic influence of social and communicative skills was 76%. Overall, twin studies have shown that autistic traits in the general population are moderately to highly heritable.

1.6.1.2 Molecular genetics

Twin studies and family studies led to the suggestion that the aetiology of ASD involves several genes. However, the identity and number of genes involved are not yet known with a review of the molecular genetic studies of ASD beyond the scope of this thesis, and the interested reader is referred to Betancur (2011) which summarises over 100 genes and 44 genomic loci implicated in the aetiology of ASD. In addition, a continually updated database of candidate genes for ASD can be found online (Basu, Kollu, & Banerjee-Basu, 2009).

The importance of the contribution of molecular genetics to understand the aetiology of autism commenced with the identification that many rare and genetic conditions are associated with autism such as tuberous sclerosis complex, Fragile X syndrome, Down syndrome, Angelman and Prader-Willi syndrome to name a few. For example, tuberous sclerosis complex (TSC) is a rare genetic disorder which causes non-malignant tumours in the body and is caused by a mutation in one of two genes, TSC1 (chromosome 9q34) and TSC2 (chromosome 16p13). The prevalence of autism in tuberous sclerosis complex is estimated from 16% to over 65% (Smalley, 1998; Wong, 2006). Additionally, Fragile X Syndrome is a genetic disorder caused by a trinucleotide repeat expansion in the gene FMR1 at Xq27.3. The prevalence of autism in Fragile X syndrome is estimated between 25% and 33% (Bailey et al., 1998; Rogers, Wehner, & Hagerman, 2001). Moreover, Angelman syndrome is associated with disruption to a maternal gene UBE3A at 15q11.2, with a lack of paternal contribution within the same region (15q11-13)

leading to Prader-Willi syndrome. The prevalence of autism is 42% in Angelman syndrome (Peters, Beaudet, Madduri, & Bacino, 2004) and 25.3% in Prader-Willi syndrome (Veltman, Craig, & Bolton, 2005). However, the comorbidity of these genetic conditions with autism is generally less than 50% (Zafeiriou, Ververi, & Vargiami, 2007). Although these syndromic forms of ASD provide evidence for a genetic basis of autism, they only account for 1% of ASD cases.

Some ASD cases are due to rare variants that have large effects, while a larger percentage of ASD cases are due to a combination of common variants that exert small effects. The contribution of rare genomic variants in ASD was first offered by studies investigating chromosomal abnormalities (Christian et al., 2008). The association between *de novo* copy number variations (CNVs) and ASD followed, accounting for nearly 10% of individuals diagnosed with ASD (Sebat, 2007). A higher frequency of *de novo* CNVs in simplex (10%) versus multiplex (3%) and controls (1%) has been reported (Sebat et al., 2007), suggesting that ASD is more likely to arise *de novo* in simplex families and inherited through common variants in multiplex families. Pinto et al. (2010) described the involvement of multiple rare CNVs, both genome-wide and at specific loci, in ASD. The CNVs implicated many novel ASD genes, and these CNVs disrupted certain gene pathways. In addition, Marshall et al. (2008) found CNVs in 44% of ASD families, with most CNVs inherited and some with *de novo* alterations.

Common variants are defined as those found in more than five percent of the population. Genome-wide association studies were designed to detect these common variants. However, they have largely been unsuccessful in identifying single nucleotide polymorphisms (SNPs) associated with ASD. Using a GWAS approach, Anney et al. (2012) did find an association between a SNP located within CNTNAP2, a gene previously identified as an ASD susceptibility gene. Authors concluded that common variants contribute significantly to ASD. Additionally, a recent study indicated that common genetic variants may contribute about half the risk of developing ASD, compared to just 3% for rare variants (Gaugler et al., 2014).

The theory of defective synaptic function has been hypothesised to link rare and common variants at the level of biological function (Zoghbi, 2003). Moreover, it has been suggested that deficits in synaptogenesis may increase risk for ASD (Bourgeron, 2009). Additionally, a significant number of genes that are essential for synaptogenesis and synaptic function have been recently associated with ASD (Mitchell, 2011). Disruption in certain synaptic gene

pathways may lead to deficits in synaptogenesis during neurodevelopment, leading to the phenotype of ASD. Furthermore, Awadalla et al. (2010) investigated 401 synaptic genes in a large cohort of ASD and schizophrenic individuals and discovered 14 unique *de novo* mutations. The analyses showed that there was a significantly higher proportion of deleterious *de novo* mutations in synaptic genes compared to non-functional regions within the ASD and schizophrenic cohorts, suggesting a role of *de novo* mutations in synaptic genes in the aetiology of ASD.

1.6.1.3 Epigenetics

Monozygotic twins share the same genome. However, monozygotic twins are not phenotypically identical, and have widespread differences in their epigenome (Fraga et al., 2005). Epigenetic changes are chemical modifications when methyl and other chemical groups attach to DNA or histones that DNA is wrapped around, and these modifications control when and where genes are expressed, i.e., epigenetic changes can turn genes on or off. These epigenetic changes regulate the amount of RNA and protein that is produced without changing the genome. Epigenetic errors can occur as primary stochastic events or as secondary events due to genetic mutations or environmental factors such as diet, stress or toxins. Potential epigenetic aetiologies of ASD involve both genetic and environmental factors.

Epigenetic markers have a key role in normal development, including neuronal development, and have been linked to many disorders including ASD. The epigenetic aetiology of ASD is a recent and emerging field (see Grafodatskaya, Chung, Szatmari, and Weksberg, 2010, for an initial review of the field). Shulha et al. (2012) investigated histone methylation in post-mortem brains of individuals with and without ASD. Abnormal epigenetic markers were found on or near known autism risk genes, indicating that a subset of autism susceptibility genes carrying strong penetrance for ASD could be epigenetically dysregulated. In addition, Schroeder, Lott, Korf, and LaSalle (2011) generated a genome-wide pattern of methylation in neurons and found that autism candidate genes were over-represented in areas with high levels of methylation. It was proposed that there may be epigenetic dysregulation of genes that are related to the neuronal synapse in ASD.

As indicated in twin studies of ASD, there is still substantial discordance in MZ twin pairs for a diagnosis of ASD and also for symptom severity within ASD-concordant MZ twin pairs. Wong et

al. (2014) used this as a model to investigate the role of non-genetic epigenetic factors in the aetiology of ASD using a genome-wide approach. There were numerous DNA methylation differences in MZ twins discordant for ASD and ASD-related traits highlighting a role for the non-shared environment in the aetiology of ASD. In addition, there was a correlation between DNA methylation and autism symptom severity, suggesting a quantitative relationship between severity of the autism phenotype and epigenetic modifications. The study also found DNA methylation differences in MZ discordant twins that were specific for certain symptom domains. For example, a gene that encodes the GABA receptor, which has been linked to ASD, was found to be differentially methylated in twin pairs discordant for social traits. Interestingly, the authors suggested that there is a potential for epigenetic biomarkers to be used as predictors of the severity of autism symptoms.

1.6.2 Environment

The twin study by Hallmayer, et al. (2011) proposed a larger role for environmental factors than had previously been suggested. In addition, epigenetic research has suggested potential gene-environment interactions in ASD (Wong, et al., 2014). This may highlight the role of environmental risk factors for ASD, especially during the pre-, peri- and neonatal periods when neurodevelopment proliferates.

Guinchat et al. (2012) conducted a systematic review of case-control studies to estimate the impact of pre-, peri- and neonatal factors on the risk for ASD. A total of 85 studies were analysed. Firstly, the familial risk factors identified were advanced maternal age or paternal age, being firstborn vs. thirdborn (or later) and the mother's status as foreign born. Secondly, the prenatal risk factors identified were bleeding, medication during pregnancy, diabetes, with limited evidence for maternal infection, pre-eclampsia and stress. Thirdly, the perinatal risk factors identified were preterm birth, breech presentation, and planned caesarean section. Lastly, the neonatal risk factors identified were low Apgar scores, neonatal encephalopathy, hyperbilirubinemia, birth defects and baby small for gestational age, with limited evidence for low birth weight. Overall, no individual factor was consistently validated as a risk factor for ASD. Therefore, several risk factors in the pre-, peri- and neonatal periods may increase risk for ASD.

Another potential environmental risk factor for ASD is environmental toxicants. Rossignol, Genuis, and Frye (2014) systematically reviewed studies investigating the association between

ASD and environmental toxicants, examining 128 studies conducted preconception, during gestation or in childhood. Environmental toxicants implicated in ASD included pesticides, phthalates, polychlorinated biphenyls, solvents, toxic waste sites, air pollutants and heavy metals, with the strongest evidence found for air pollutants and pesticides. The majority of studies (92%) that examined a potential association between ASD and environmental toxicant exposure reported a significant relationship. Half of the studies investigating the concentrations of heavy metals as biomarkers in children with ASD found elevated levels in ASD compared to controls. In addition, seven studies reported that these biomarkers were associated with ASD severity. Overall, the studies reviewed by Rossignol, et al. (2014) support an association between environmental toxicants and ASD.

An interesting study examined the association between inter-pregnancy interval and the risk of ASD (Risch et al., 2014). The study found that an inter-pregnancy interval of less than 24 months was associated with increased odds of ASD in second-born children. The greatest risk was when the inter-pregnancy interval was less than 12 months. One explanation offered by the authors was that a short inter-pregnancy interval could be associated with nutritional depletion. However, this intriguing finding awaits replication.

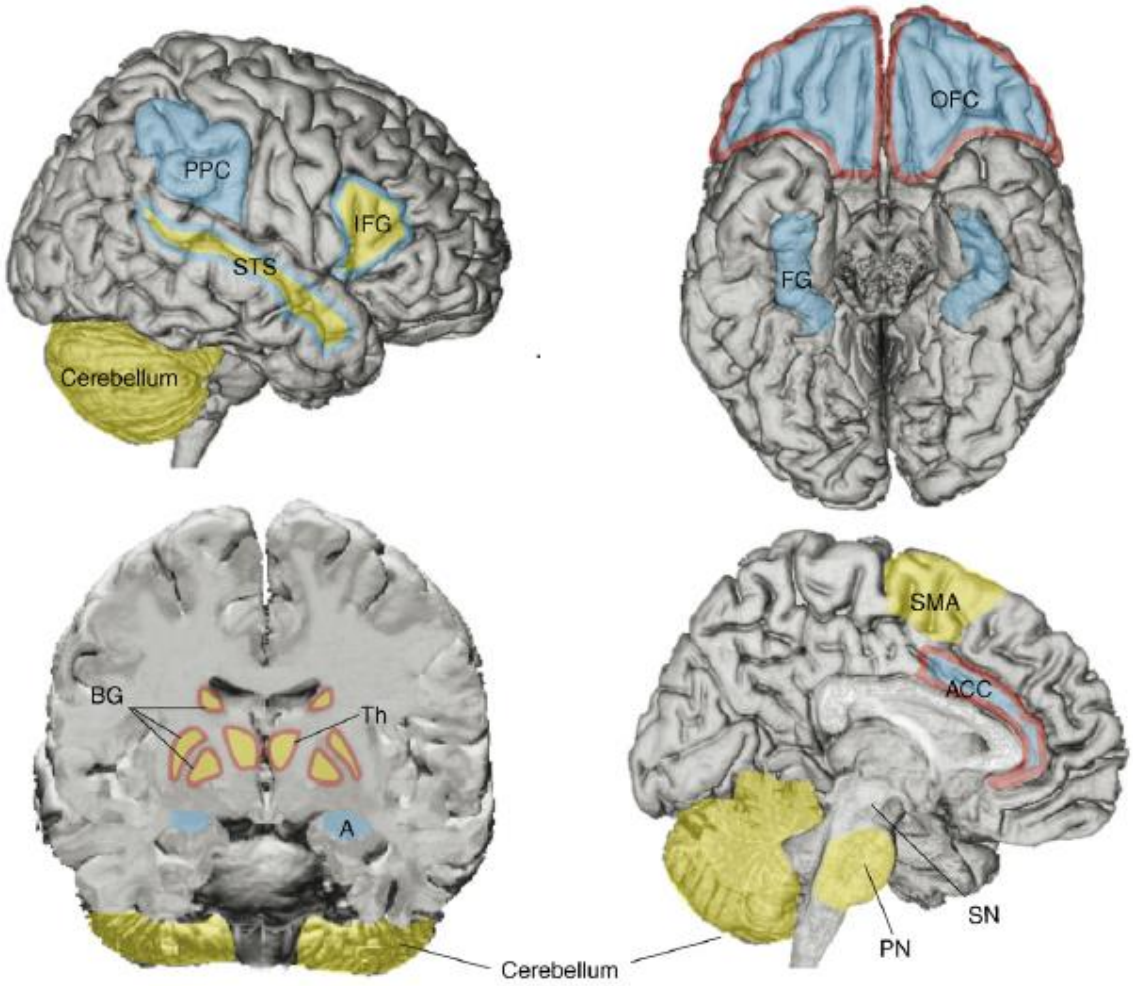
There are likely to be complex interactions between genetic and environmental factors conferring in risk for ASD. For example, individual variability in genetic susceptibility for ASD may lower the threshold at which environmental factors have influence. Therefore, genetic and environmental factors may work interdependently during critical periods in development to increase the likelihood of developing ASD.

1.6.3 Neurobiological

The neurobiology of ASD has been researched extensively over the past 35 years, with suggestions that ASD involves changes in regional brain anatomy and functional neural networks (Akshoomoff, Pierce, & Courchesne, 2002; DiCicco-Bloom et al., 2006; Minshew & Williams, 2007; Pardo & Eberhart, 2007; Parellada et al., 2014; Polleux & Lauder, 2004). Neuropathological and neuroimaging approaches have been used to identify these underlying brain regions, neural networks, and cellular systems that are implicated in ASD, and are briefly summarised here.

The neurobiological account of ASD began with the consistent finding of macrocephaly (larger head circumference; Courchesne et al., 2001) and megencephaly (larger brain volume) in ASD. An increase in brain volume in ASD has been observed in the first and second year of life in around 25-30% of children with ASD, and these differences reduce by late childhood/adolescence (Redcay & Courchesne, 2005). In addition, Sparks et al. (2002) found that 3- to 4-year old children with ASD showed an increase in the volume of the cortex and cerebellum, and in the amygdala. Various hypotheses have been proposed to explain the abnormal rapid growth in frontal, temporal, and parietal lobes in young children with ASD, such as increased dendritic branching, reduced synaptic pruning and increased number, size, or myelin content of glia. In addition, decreased numbers of cerebellar Purkinje cells and changes in the mini-columnar organisation in cortical regions have been consistently reported in ASD (DiCicco-Bloom, et al., 2006). Defects in the brainstem and cerebellum, the limbic system and the cortex have been implicated in ASD.

Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) are useful approaches to examine the neural networks affected in ASD. The three core symptom domains likely involve extensive neural networks, highlighted in Figure 1.2 (Amaral, Schumann, & Nordahl, 2008). Pelphrey, Adolphs, and Morris (2004) reviewed three brain regions involved in different aspects of social functioning that may be implicated in the social impairments in ASD. Briefly, the review outlined that: (1) there are functional abnormalities in amygdala activity in ASD (Critchley et al., 2000) and amygdala size is correlated with the severity of social impairment (Schumann, Barnes, Lord, & Courchesne, 2009); (2) there are decreases in grey matter concentration in the superior temporal sulcus (Boddaert et al., 2004), and this region is less activated by faces in ASD (Scherf, Luna, Minshew, & Behrmann, 2010); and (3) the fusiform gyrus is less activated for faces in ASD (Critchley, et al., 2000; Hubl et al., 2003; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000). The neurobiological basis of restricted and repetitive behaviours has been less studied than the social-communicative symptoms, with a focus on the larger volume of basal ganglia and striatum, abnormalities in the anterior cingulate cortex, and atypical caudate-cortical connectivity (for review see Langen, Durston, Kas, van Engeland, & Staal, 2011).



Social impairment	Communication deficits	Repetitive behaviors
OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala mirror neuron regions IFG – Inferior frontal gyrus PPC – Posterior parietal cortex	IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei cerebellum	OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus

Figure 1.2. Brain areas associated with the three symptom domains of ASD (taken from Amaral, et al., 2008)

One brain-based theory of ASD called the 'broken mirror theory' involves dysfunction in the mirror neuron system (Dapretto et al., 2006; Hamilton, 2013; Williams, Whiten, Suddendorf, & Perrett, 2001). The mirror neuron system is defined as the set of brain regions which are active both when a person performs an action, and when they observe another person perform the same action, and so is suggested to be involved in self-other mapping. It has been claimed that

this dysfunction of the mirror neuron system causes social and communication impairments in ASD (Williams, et al., 2001). However, support from neuroimaging studies is limited (Hamilton, 2013).

The cortical under-connectivity theory of ASD is a prominent brain-based theory that postulates abnormalities in the connectivity of neural systems in ASD. The first evidence of under-connectivity was found in an fMRI study using a language comprehension task (Just, Cherkassky, Keller, & Minshew, 2004). Just, et al. (2004) found poor synchronisation of the activation across cortical areas in ASD during the task, and so proposed that ASD is caused by under-functioning integrative circuitry that leads to abnormalities in the integration of information at the neural and cognitive levels. This under-connectivity has primarily been reported between the prefrontal cortex and posterior brain regions (for a recent review, see Maximo, Cadena, & Kana, 2014). This poor prefrontal-posterior connectivity could underlie the social and communication impairments in ASD due to a lack of integration of different types of information at a high level (Just, et al., 2004), with support from the finding of a negative relationship between symptom severity and the functional connectivity in the frontal-parietal network (Just, Cherkassky, Keller, Kana, & Minshew, 2007).

Under-connectivity has been reported in ASD between other brain regions and there have also been several studies in ASD that report over-connectivity between brain regions (reviewed in Maximo, et al., 2014). These enhanced connections may be linked to the increase in brain volume previously mentioned. Higher functional connectivity has been associated with more severe restricted, repetitive behaviours (Agam, Joseph, Barton, & Manoach, 2010; Monk et al., 2009). Recently, Hahamy, Behrmann, and Malach (2015) found both over- and under-connectivity in ASD compared to controls. The more idiosyncratic an individual's pattern of connectivity was (as compared to controls), the more severe their symptoms of ASD were. Overall, abnormalities in functional connectivity appear to be a core characteristic of ASD, and are related to the severity of symptoms.

1.7 Cognitive Theories

Seminal experimental studies in ASD were conducted by Hermelin and O'Connor during the 1960s. Early cognitive work focussed on impairments in perception, memory & language in ASD

(reviewed by Prior, 1979). In the 1980s, a primary cognitive deficit was proposed to underlie the behavioural phenotype of ASD (Rutter, 1983). Rutter (1983) described one individual with ASD who was unable to "mind-read", i.e., he could not read other people's thoughts. This description is perhaps a precursor to the pioneering cognitive deficit hypothesis of ASD, otherwise known as the 'Theory of Mind' hypothesis, which has been highly influential in psychological research.

This pioneering cognitive theory of ASD (discussed below) led the way for the proposal of other cognitive theories over the past thirty years. These cognitive theories of ASD can be broadly divided into domain-specific and domain-general theories. Domain-specific theories situate the primary deficit in social processing. Prominent amongst these is the 'Theory of Mind' deficit account, which explains the social and communication impairments of ASD as resulting from difficulty representing mental states (e.g., Frith, Morton, & Leslie, 1991). Domain-general accounts of ASD propose that the primary deficit/difference is not in social cognition specifically but lies in, for example, 'executive functions' (EF; Hill, 2004). A number of domain-general accounts suggest areas of superior processing or differences in cognitive style, such as 'weak central coherence' (Frith, 1989; Happé & Booth, 2008; Pellicano, 2010a), a bias towards featural processing and reduced configural processing. Superior local processing, but accompanied by intact global processing, is also proposed by 'enhanced perceptual processing' (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006), 'systemising' (Baron-Cohen, 2009) and enhanced discrimination (O'Riordan & Plaisted, 2001) accounts of ASD. The three main cognitive theories of ASD, theory of mind deficit, executive dysfunction, and weak central coherence (reviewed in Rajendran & Mitchell, 2007), are the primary focus of this thesis.

1.7.1 Social-Cognitive Theories

1.7.1.1 Theory of Mind

The initial definition of a theory of mind was provided by Premack and Woodruff (1978) as the way in which an individual infers their own and others' mental states that are not directly observable and these inferred mental states (e.g., beliefs, desires) are used to predict or explain the behaviour of others. Subsequently, Wimmer and Perner (1983) introduced the 'false-belief' unexpected transfer task to test when young children develop a theory of mind. In this task, a character places an object in location x. In the absence of the character, the object is transferred from x to location y. Participants are then required to indicate where the character

will look for the object; in location y (where the object is currently located) or location x (where the character thinks the object is). Wimmer and Perner (1983) used the unexpected transfer task to show that children's theory of mind ability emerges between the ages of 4 and 6 years.

Baron-Cohen, Leslie, and Frith (1985) investigated whether a deficit in theory of mind could explain the social impairment in ASD. In their study, 80% of children with autism failed Wimmer and Perner's (1983) unexpected transfer false-belief task compared to 15% and 14% of typically-developing children and children with Down's syndrome (respectively). Baron-Cohen, et al. (1985) concluded that children with autism lack a theory of mind and are unable to attribute beliefs to others and cannot predict the behaviour of other people. This seminal study to show that children with autism have an inability to attribute false-beliefs has been extensively replicated (Baron-Cohen, 1991; Fisher, Happé, & Dunn, 2005; Grant, Grayson, & Boucher, 2001; Luckett, Powell, Messer, Thornton, & Schulz, 2002; Yirmiya, SolomonicaLevi, Shulman, & Pilowsky, 1996), using various tasks such as unexpected contents tasks (Charman & Baron-Cohen, 1992; Charman & Lynggaard, 1998; Perner, Frith, Leslie, & Leekam, 1989; Williams & Happé, 2009), mental state stories (Tager-Flusberg & Sullivan, 1994b) and deception tasks (Baron-Cohen, 1992; Russell, Mauthner, Sharpe, & Tidswell, 1991; Sodian & Frith, 1992; Yirmiya, et al., 1996).

Some individuals with ASD pass first-order false belief tasks, which poses a problem for the universality of the theory. Yirmiya, Erel, Shaked, and Solomonica-Levi (1998) conducted a meta-analysis of theory of mind tasks and found that a theory of mind deficit characterised most individuals with ASD, but this deficit was not unique to ASD as individuals with intellectual disability also exhibited a theory of mind deficit. Instead, individuals with ASD may have a more severe impairment in theory of mind ability.

To account for the 20% of individuals with autism who passed the first-order false-belief task (Baron-Cohen, et al., 1985), Baron-Cohen (1989) examined the ability to pass a higher-level theory of mind task. This higher level task involved second-order false-belief understanding, i.e., the ability to think what another person thinks about a third person. Children with ASD who passed first-order false-belief tasks were impaired on the second-order false-belief task relative to typically-developing children and children with Down's syndrome. Baron-Cohen (1989) suggested that theory of mind development is very delayed in children with autism by seven

chronological years, instead of an absolute lack of theory of mind ability. This was supported in a large-scale empirical study of theory of mind abilities in ASD (Happé, 1995). A two-threshold model was proposed in which the lower-bound of verbal mental age to pass false-belief tasks is two years, ten months for typically-developing children compared to five years, six months for children with ASD. Therefore, the theory of mind deficit in ASD may not be absolute, but rather may be revealed in a severe developmental delay.

Bowler (1992) found that 73% of individuals with Asperger's syndrome were able to solve a second-order false-belief task. However, when these individuals were asked to explain their answers, they did not use mental state terms. Additional studies have found that children with autism who passed first-order false-belief tasks also passed second-order false-belief tasks (Leekam & Prior, 1994; Tager-Flusberg & Sullivan, 1994a). It was suggested that individuals with ASD use logical cognitive processes to solve false-belief tasks (Bowler, 1992; Frith, Happé, & Siddons, 1994; Williams & Happé, 2009), may have difficulty applying conceptual knowledge (Leekam & Prior, 1994) or that second-order tasks are too complex and may rely on information processing ability (Tager-Flusberg & Sullivan, 1994a). To add, Senju, Southgate, White, and Frith (2009) found that individuals with Asperger's syndrome passed both false-belief and more advanced theory of mind tasks. However, these individuals did not spontaneously attribute belief status to others in a nonverbal false-belief task. This reveals that although some individuals with ASD can reason explicitly about false-beliefs (perhaps through compensatory learning), they still have a persistent impairment in spontaneous mentalising.

Baron-Cohen, O'Riordan, Stone, Jones, and Plaisted (1999) suggested that passing first- and second-order false-belief tasks is a relatively early stage in theory of mind development and that theory of mind continues to develop beyond four to six years of age in typical development. Therefore, a theory of mind should not be regarded as either absent or present, but as quantifiable with a certain threshold of theory of mind needed to be attained in order to pass developmentally appropriate tasks. In addition, Yirmiya, et al. (1998) proposed that theory of mind should not be conceptualised as an 'all-or-nothing' phenomena.

Several more advanced tests of theory of mind have been established to test theory of mind ability beyond simple false-belief understanding, such as the Eyes Task (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001),

Recognition of Faux Pas test (Baron-Cohen, et al., 1999), Strange Stories test (Happé, 1994c; White, Hill, Happé, & Frith, 2009), and a triangle animation task (Abell, Happé, & Frith, 2000; Castelli, Happé, Frith, & Frith, 2000; White, Coniston, Rogers, & Frith, 2011). Using the Eyes Task as a measure of theory of mind ability, it has been shown that males and females are equally impaired in theory of mind ability in autism (Lai et al., 2012). In addition, Brent, Rios, Happe, and Charman (2004) investigated the associations between performance in three more advanced tests of theory of mind in children with autism and typically-developing controls. A distinction was made between social-cognitive and social-perceptual aspects of mentalising, with the suggestion that mentalising abilities may be more fractionated in autism.

The brain basis for a theory of mind has also been studied. One of the first functional neuroimaging studies of theory of mind found a specific pattern of activation in the left medial frontal gyrus during mental state attribution with increased levels of activation in the posterior cingulate cortex and the right inferior parietal cortex at the temporo-parietal junction (Fletcher et al., 1995). To further clarify this finding, an fMRI study found that brain activation during theory of mind tasks was increased in the medial prefrontal cortex (Gallagher et al., 2000), suggesting that the ability to mentalise is mediated by this brain region. Subsequently, Castelli, et al. (2000) investigated brain activation during the spontaneous attribution of mental states. Increased activation for mental state attribution was found in a network of brain regions, including the medial prefrontal cortex, the temporal pole adjacent to the amygdala and the temporo-parietal junction, and these brain regions have been implicated in the theory of mind brain network.

The theory of mind brain network may be dysfunctional in ASD. One of the first neuroimaging studies in ASD found less activation in the medial prefrontal cortex in participants with ASD during a mentalising task (Happé et al., 1996). Castelli, Frith, Happe, and Frith (2002) found greater activation during mental state attribution in the medial prefrontal cortex, the temporal pole adjacent to the amygdala, and the superior temporal sulcus at the temporo-parietal junction. In comparison, there was less activation in these three brain regions of the theory of mind network in ASD. In addition, there may be frontal-posterior underconnectivity in the theory of mind network in ASD (Kana, Keller, Cherkassky, Minshew, & Just, 2009). Therefore, there is atypical activation of brain regions in ASD that are involved in theory of mind.

Some of the limitations of research into theory of mind have been identified, such as the verbal nature of tasks, the explicit nature of task presentation and the 'all-or-nothing' approach to performance in theory of mind tasks. Klin (2000) attempted to reduce these factors by using silent cartoon animations in which geometric shapes performed social actions. When asked to describe these animations, typically-developing individuals provided narratives that attributed social meaning indicating a spontaneous predisposition to perceive social meaning, even in geometric shapes. However, individuals with ASD who had previously passed second-order false-belief tasks provided either irrelevant descriptions or purely geometric accounts of the cartoons. To explain these results, Klin, Jones, Schultz, and Volkmar (2003) proposed a new framework termed the 'Enactive Mind' account. Central to the Enactive Mind account is the role of social motivation which predisposes the development of a theory of mind. This approach proposes that social stimuli are salient in typical development. However in ASD, social stimuli are not as salient and so physical stimuli attract attention leading to a specialisation in things rather than people. Whether theory of mind deficits are primary or whether they result from earlier abnormalities of social orienting or social motivation, has also been a topic of much debate (Dawson, Webb, & McPartland, 2005; Jones, Carr, & Klin, 2008).

1.7.2 Non-Social Cognitive Theories

1.7.2.1 Executive Function

Executive function is a multi-faceted construct, intended to include planning, initiation, shifting, monitoring and inhibition of behaviours. Kenworthy, Yerys, Anthony, and Wallace (2008) defined executive function as a "set of cognitive processes that direct behaviour regulation and orchestration of attaining a future goal". Burgess, Alderman, Evans, Emslie, and Wilson (1998) found that there were three underlying cognitive factors to executive function tests; inhibition (supressing a habitual response), intentionality (creating and maintain goal-directed behaviours) and executive memory (shifting attention). Ozonoff, Pennington, and Rogers (1991) suggested that ASD could be explained as a deficit in executive function as individuals with ASD show inflexible and perseverative behaviours with narrow interests that could reflect underlying problems with shifting behaviours. In addition, they may act impulsively, indicating problems with inhibition.

Hill (2004) provided a comprehensive review of cognitive behavioural studies of executive function in ASD, specifically focussing on planning, flexibility, and inhibition. Firstly, planning involves the sequencing of actions, and monitoring, re-evaluating and updating these actions. Individuals with ASD have been found to be impaired on tasks that assess planning ability, relative to typically developing controls, such as the Tower of London/Hanoi task (Bennetto, Pennington, & Rogers, 1996; Hughes, Russell, & Robbins, 1994; Ozonoff & Jensen, 1999; Ozonoff, et al., 1991). Secondly, mental flexibility involves the ability to implement, track and change cognitive strategies. Set-shifting is a form of mental flexibility and involves the process of updating a cognitive strategy, e.g., abandoning an old rule to implement a new rule. Two similar tasks in which individuals with ASD have been shown to have poor mental flexibility are the Wisconsin Card Sorting Task and the intradimensional/extradimensional task (ID/ED), in which individuals with ASD appear to have difficulties set-shifting and exhibit perseverative errors (Bennetto, et al., 1996; Hughes, et al., 1994; Liss et al., 2001; Ozonoff & Jensen, 1999; Ozonoff, et al., 1991; Shu, Lung, Tien, & Chen, 2001). Finally, inhibitory control involves selectively ignoring responses to inappropriate stimuli. Individuals with ASD have been found to be unimpaired on the Stroop task (Goldberg et al., 2005; Ozonoff & Jensen, 1999), unimpaired on negative priming (Brian, Tipper, Weaver, & Bryson, 2003; Ozonoff & Strayer, 1997), impaired on prepotent inhibition and cognitive flexibility conditions of Go/No-Go tasks (Ozonoff, Strayer, McMahon, & Filloux, 1994), perseverative on Windows and Detour-Reaching tasks (Russell, Hala, & Hill, 2003; Russell, et al., 1991) and impaired on Luria Hand Game (Hughes, 1996); overall suggesting difficulties in the inhibition of prepotent responses.

Executive functions in general have been linked to the frontal structures of the brain, and in particular to the prefrontal cortex. The frontal-parietal network seems to be key for executive functions. Functional neuroimaging studies have found atypical brain activity in individuals with ASD when performing various executive function tasks (Just, et al., 2007; Kana, Keller, Minshew, & Just, 2007; Schmitz et al., 2006; Solomon et al., 2009). For example, Just, et al. (2007) found lower activation between frontal and parietal regions for individuals with ASD during the Tower of London task using fMRI. There appears to be lower levels of functional connectivity in the frontal-parietal network in ASD that is crucial for executive functions (Just, et al., 2007; Solomon, et al., 2009).

Many studies investigating executive function in ASD have been conducted at a single time point. The developmental trajectories of different aspects of executive function are needed as the prefrontal cortex, which mediates executive function, shows a protracted developmental trajectory throughout childhood and into adolescence (Casey, Giedd, & Thomas, 2000). Furthermore, Pellicano (2012) suggested that individual differences in executive function abilities could explain some of the variability in outcomes for children with ASD. Ozonoff and McEvoy (1994) conducted one of the first longitudinal studies to investigate executive function development in ASD. The ASD group did not improve in their executive function skills over a three year period, compared to an overall improvement in the control group. Therefore, executive function ability remained stable and static throughout development in ASD in this study. Happé, Booth, Charlton, and Hughes (2006) investigated age-related differences in a battery of executive functioning tasks for ASD, ADHD and typically-developing groups. In both the ASD and the typically-developing group, the older participants (11-16 years-old) outperformed the younger participants (8-10 years-old) on several executive function tasks. This is in contrast to Ozonoff and McEvoy (1994) findings, but could be explained by the differences in age across the two studies, with Happé et al.'s (2006) study containing a younger age group. Pellicano (2010a) examined the development of executive function even earlier in childhood, from 5- to 8-years-old. The ASD group's planning ability significantly improved over this 3 year period, and improved at a faster rate than in the typically-developing group. This study suggests that executive function becomes less marked with age. However, executive function may not fully mature in ASD (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007) with a greater divergence from typical development over time (Rosenthal et al., 2013). Overall, executive function may improve through childhood and adolescence, but may not reach adult levels in ASD.

The uniqueness of executive function deficits to ASD can be questioned as executive deficits are also found in ADHD (Pennington & Ozonoff, 1996), schizophrenia (Velligan & Bow-Thomas, 1999), and obsessive-compulsive disorder (OCD) (Olley, Malhi, & Sachdev, 2007). However, a differing executive function profile may define ASD. For example, Ozonoff and Jensen (1999) found that ASD was characterised by impaired planning and flexibility, compared to impaired inhibition in ADHD. In addition, individuals with ASD had elevated scores across executive function domains, and these scores were significantly higher for the shifting domain compared

to other clinical groups (ADHD, reading difficulties, and traumatic brain injury) (Gioia, Isquith, Kenworthy, & Barton, 2002). Happé, Booth, et al. (2006) examined the executive function profiles in ASD versus ADHD. Poor response selection/monitoring typified ASD compared to greater inhibition problems in ADHD. In contrast, Johnson (2012) argued that executive deficits are not core to developmental disorders. Instead, individuals with good executive function skills may be able to compensate or better adapt to atypicalities in neural functioning.

Another issue with the executive function deficit hypothesis is that it is not universal in ASD. Many studies focus on group differences, comparing clinical groups with typically-developing controls, and so may mask any individual differences in executive function within ASD. Taking a group difference approach assumes that each group has a homogeneous cognitive profile. For example, 41% of the ASD group performed within the normal range on a task measuring perseveration, yet group differences were reported (Ozonoff & McEvoy, 1994). Furthermore, executive function deficits characterised only half of children with ASD (Pellicano, Maybery, Durkin, & Maley, 2006). Therefore, not all individuals with ASD have executive function deficits, and so it could be argued that it is not a core feature of the disorder, but is instead commonly associated with ASD (Liss, et al., 2001).

The lack of specificity of the 'executive functions' may also explain the mixed results in the literature. There is a lack of consensus regarding the definition of 'executive functions'. Executive function is a multi-faceted construct with processes that are difficult to delineate. Some accounts present a unitary construct, whereas others suggest a fractionated model of executive function (e.g., Burgess, et al., 1998). Some of the differences between studies investigating the developmental trajectory of executive function in ASD may be hindered by the multiple processes of executive function that mature at different times. In addition, cognitive tasks purported to measure singular aspects of executive function also require many other executive function processes to complete. For example, the traditional tower tasks that are suggested to measure planning ability also require working memory, the inhibition of prepotent responses, and the generation of problem-solving ideas (Hill & Bird, 2006). Therefore, the outcome of many executive function tasks is in fact the sum of performance across a number of executive processes. Overall, the executive dysfunction hypothesis of ASD has been challenged regarding its issues of specificity, uniqueness and universality.

1.7.2.2 Weak Central Coherence

The weak central coherence account of ASD proposes a specific perceptual cognitive style in which there is a processing bias for local details over a preference to perceive the global form. In 1989, Frith introduced the idea that there is a drive for coherence in typically developing children and adults, defined as the tendency to integrate large amounts of information (Frith, 1989). It was proposed that this drive for coherence is diminished in ASD, i.e., individuals with ASD show 'weak central coherence'. In 2003, Frith updated the weak central coherence account, proposing that the drive for global coherence, that is inbuilt in typical development, is weak in ASD, with an inability to integrate local details into a coherent whole and a drive towards local details (Frith, 2003). This proposal is evident in Kanner's (1943) original description of autism, stating that children with autism appear to have an "inability to experience wholes without full attention to the constituent parts" (p. 246). In addition, ASD self-advocates and parents of individuals with ASD have supported this concept. For example, Temple Grandin (2013) stated that "the tendency to see details before I see the bigger picture has always been a central feature in how I relate to the world" (p.120). The central coherence account has been modified with an emphasis on a different cognitive style, rather than a deficit, in which individuals with ASD have superior local processing and have a decreased tendency to integrate information (Happé & Booth, 2008). Therefore, the weak central coherence account predicts that individuals with ASD will have good performance on tasks which attention to local details and/or not paying attention to context is advantageous, and poor performance on tasks which require integration of information using context, or involve the perception of global meaning.

Happé and Frith (2006) provided a review of the empirical studies investigating weak central coherence in ASD. In the perceptual domain, individuals with ASD have been found to be less susceptible to visual illusions (Happé, 1996). In contrast, Ropar and Mitchell (1999) investigated this phenomenon using a different response method and found that individuals with ASD are susceptible to visual illusions. It was acknowledged that illusions are different as susceptibility to them is not a deliberate act and so the results do not necessarily conflict with the weak coherence account. Jarrold and Russell (1997) investigated the counting strategies of children with ASD. When counting dots that were presented in a canonical form, children with ASD did not engage in a global form of counting. Instead of subitising, children with ASD counted each

dot separately, perhaps indicating a preference for local processing. Similarly, Brosnan, Scott, Fox, and Pye (2004) found that children with ASD had a deficit in gestalt grouping. They concluded that there is a failure in ASD to process the relationships that exist at the local level that allow the perception of coherent forms, and therefore are unable to use context.

The seminal tasks used in the visuo-spatial domain to investigate weak central coherence were the Embedded Figures Test (EFT) and the Block Design task. In the EFT, participants have to find a simple figure in a more complex array. Shah and Frith (1983) found that an autism group performed significantly better than an IQ-matched control group on this task. It was suggested that the complex shape was not as relevant for children with autism and so their search was better and faster than for the control group. Another task in which a tendency towards local over global processing is advantageous is the Block Design Task. Shah and Frith (1993) manipulated the classic Block design task to compare performance on a segmented versus an un-segmented version. The ASD group performed significantly better than controls when presented with the un-segmented version. It was concluded that the ability to perceive parts when presented as wholes is a consequence of weak central coherence in ASD. Tasks in which a tendency towards global over local processing is advantageous have also been used. For example, Jolliffe and Baron-Cohen (2001) found that individuals with ASD were less able to integrate visual elements to identify an object, suggesting impaired integration to produce a global form. To add, a more fragmented drawing style has been reported in ASD (Fein, Lucci, & Waterhouse, 1990). For example, Mottron, Belleville, and Menard (1999) found that individuals with ASD produced more local features at the start of copying a drawing compared to typically-developing controls, suggesting a bias towards local processing. This study was supported by the finding that children with ASD have a more detail-focused drawing style, i.e., they were more likely to start drawing with a local feature, drew in a fragmented manner, and their drawings contained violations to configurations in comparison to typically-developing children's drawings (Booth, Charlton, Hughes, & Happé, 2003). Another visuo-spatial task is the Navon task in which a large letter shape is presented (global level) that is made up of smaller letters (local level) and participants are required to identify the letters at the global or local level. Typically-developing individuals made more errors at the local than global level ('global advantage' effect) and were slower at identifying local letters ('global interference' effect) showing an overall 'global precedence' effect. In contrast, individuals with ASD showed a local

advantage and a local interference effect indicating diminished global processing and supporting the weak central coherence account (Plaisted, Swettenham, & Rees, 1999).

Verbal-semantic tasks have also indicated weak central coherence in ASD. For example, the Homographs Reading test involves reading homographs before or after a disambiguating sentence context, e.g., 'In her eye/dress there was a big *tear'* (Frith & Snowling, 1983). Happé (1997) used the Homographs Reading test and found that the ASD group failed to use the preceding sentence context to inform pronunciation compared to the control group. Jolliffe and Baron-Cohen (1999) also supported these results. In addition, they found that an ASD group were less likely than a control group to select a coherent inference and were also less likely to use context to interpret an auditory ambiguous sentence. Another verbal task to investigate weak central coherence is the Sentence Completion task, which involves providing one word to complete a sentence. For example, the participant will be told *"The sea tastes of salt and …"*, and asked to provide a word to complete the sentence with a local response being *"pepper*", and a correct global response being "*seaweed*". In this task, Booth and Happé (2010) found that an ASD group produced significantly more local completions than the control group. Lastly, Jolliffe and Baron-Cohen (2000) investigated whether individuals with ASD could make context-appropriate explanations for a story and found that a difficulty to extract information from context characterised the majority of those with ASD, providing support for the weak central coherence account.

To end, a recent study has investigated whether there is a local bias and reduced global interference in ASD in the auditory domain (Bouvet, Simard-Meilleur, Paignon, Mottron, & Donnadieu, 2014). In a melodic decision task, participants had to decide whether the global (melody) or local level (group of notes) was rising or falling. The ASD group showed superior local processing, and a reduced global-to-local interference, indicating that weak central coherence is apparent in the auditory, as well as the visual and verbal, domain.

Several neuroimaging studies have attempted to elucidate the underlying neural mechanisms of weak central coherence. Neuroimaging studies have examined local and global processing in typically-developing individuals using fMRI. This has indicated some degree of hemispheric specialisation for local and global processing, with left hemisphere regions typically involved in local processing and right hemisphere regions in global processing (Fink et al., 1996). In ASD,

neuroimaging studies first focused on the neural correlates of enhanced local processing. Higher activation in the early stages of visual processing has been found during the EFT in ASD compared to typical-development (Manjaly et al., 2007). In addition, Lee et al. (2007) found reduced cortical involvement in ASD during the EFT. In particular, the underlying neural network differed qualitatively in ASD compared to typically-developing adolescents. A reduction in the temporo-parietal-occipital network was found in the ASD group, suggesting that there is a reduced reliance on this network in ASD. This was supported by Boelte, Hubl, Dierks, Holtmann, and Poustka (2008) in which the neural correlates in the visual cortex in the Block Design task were investigated in ASD using fMRI. There was diminished activation in V2, the first area in the visual cortex for visual association, in the ASD group compared to the typically-developing adolescents and adults. This could indicate reduced efforts to distinguish and visually segment stimuli in ASD. Overall, these neuroimaging studies suggest that enhanced local processing may be accomplished by more automatic visuo-spatial processing in ASD. In another fMRI study, local and global levels of processing were separately examined in ASD using an abstract hierarchical design task (Gadgil, Peterson, Tregellas, Hepburn, & Rojas, 2013). During locally directed attention, the ASD group exhibited higher activation in the right prefrontal cortex. During globally directed attention, the ASD group exhibited higher activation in right lateral occipital areas. In addition, there was less deactivation of the medial prefrontal cortex in ASD. The medial prefrontal cortex is part of the default mode network, which is activated in the mind's resting state. Less deactivation of this region in ASD compared to the control group in the global condition suggests that less attention is dedicated to the global level in ASD. Therefore, studies have generally supported the notion of weak central coherence in ASD at the neural as well as the cognitive level.

A challenge to the validity of the weak central coherence account is the extent to which it characterises all individuals with ASD. Again, many studies focus on group differences, and so may conceal any individual differences in differences in cognitive style. In earlier work, 85% of an ASD group exhibited peak performance on the Block Design task (Happé, 1994d). In addition, 40% of an ASD group did not show evidence of local processing bias (Booth, et al., 2003) and a quarter did not use local completions in Sentence Completion task (Booth & Happé, 2010). Therefore, not all individuals with ASD have this specific cognitive processing style. These individual differences may reflect the vast heterogeneity present in ASD. In fact,

Happé (1999) suggested that central coherence may be a cognitive style that varies along a continuum in the normal population from 'weak' to 'strong' coherence, with those with ASD at the extreme.

Another challenge to the weak central coherence account is that a local processing bias is not specific to ASD. For example, a local processing bias and global processing deficit has been implicated in schizophrenia (Chen, Nakayama, Levy, Matthysse, & Holzman, 2003; Ferman, Primeau, Delis, & Jampala, 1999). In addition, patients with anorexia nervosa showed superior performance on the EFT and poorer performance on the Homographs reading test compared to healthy controls (Lopez et al., 2008). This indicates a local processing bias and deficits in global processing in anorexia nervosa, consistent with the weak central coherence account. However, a meta-analysis of studies examining central coherence in eating disorders found poor global processing but not superiority in local processing in contrast to the studies of coherence in ASD (Lopez, Tchanturia, Stahl, & Treasure, 2008). Finally, an ADHD group did not show weak central coherence in the Sentence Completion task (Booth & Happé, 2010).

1.8 Single vs. Multiple Cognitive Models of ASD

This chapter has provided an overview of ASD, including the biological, cognitive and behavioural levels of explanation. Morton and Frith (1995) distinguished between these so called levels of discourse in explaining developmental disorders. They suggested that most developmental disorders are defined by the biological and behavioural levels. However there is a problem relating these two levels and a third level – the cognitive level - is also required (Morton & Frith, 1995).

The preceding section described the theories put forward to provide an explanation of ASD at the cognitive level. Rutter (1983) suggested that the common clustering of behavioural symptoms in ASD implies an underlying single cognitive deficit. Morton and Frith (1995) also proposed that a common single cognitive deficit defines all individuals with ASD and this cognitive deficit underlies the core symptoms of ASD. This hypothesised single cognitive deficit model is illustrated in Figure 1.3. Morton and Frith suggested that a theory of mind deficit may be the single cognitive deficit that defines ASD. However, they acknowledged that this theory

cannot account for the restricted and repetitive behaviours and interests characteristic of ASD. Instead they postulate that ASD may be explained in terms of more than one cognitive deficit.

Single deficit accounts have also had a recent resurgence, with the implication that the social and non-social features of ASD are caused by a single mechanism (e.g. de Cruys et al., 2014; Pellicano & Burr, 2012). Pellicano and Burr (2012) provided a new hypothesis that ASD was due to a failure of Bayesian inference. This hypothesis proposes that individuals with ASD have weak 'priors' (contextual information based on previous experience) so that their perception is less modulated by experience. In addition, a predictive coding error has been proposed to explain ASD (de Cruys, et al., 2014). The predictive coding hypothesis posits that individuals with ASD have a predictive impairment and so events seem to occur unexpectedly and without cause, affecting social interactions and leading to restrictive and ritualistic behaviours.

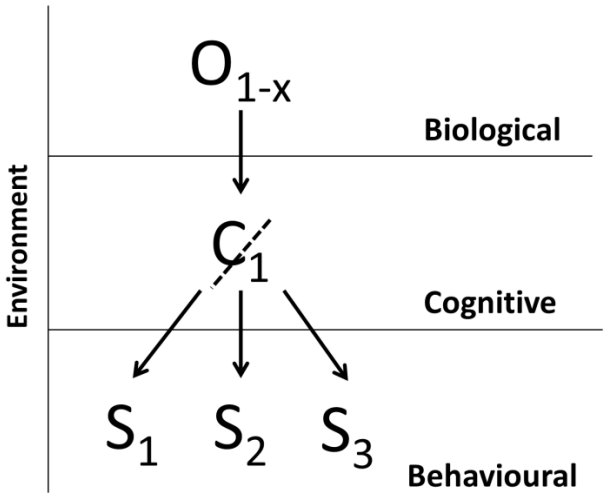


Figure 1.3. A representation of a single cognitive deficit model (Morton & Frith, 1995).

Notes: Arrows represent a causal relationship between levels. A horizontal line is used to separate levels. Hypothesised origins, O, represent genetic and brain abnormalities. The struck out C represents a cognitive domain that is found in normal development but is deficient/absent in ASD.

Pennington (2006) explored the potential of a multiple cognitive deficit model for developmental disorders. He suggested that single cognitive deficit models should be abandoned because behaviourally defined developmental disorders do not have single causes at the biological or cognitive levels and developmental disorders are often comorbid due partly to shared genetic and cognitive risk factors. Instead, he proposed a multiple cognitive deficit model of

developmental disorders that: 1) recognises the multifactorial aetiology of behavioural disorders which involve the interaction of multiple risk and protective factors; 2) these risk and protective factors alter the development of cognitive functions that are essential for normal development, and so produce the behavioural symptoms that define the disorder; 3) no single aetiological factor is sufficient for a disorder; 4) comorbidity between developmental disorders is expected due to shared aetiological and cognitive risk factors; and 5) the liability distribution for a disorder is continuous and quantitative. The complexities in moving from single to multiple cognitive deficit models was acknowledged, including issues in specification and testing of these models. Pennington et al. (2012) tested single and multiple cognitive deficit models in dyslexia and found that a hybrid model was the best fit with multiple possible pathways to the disorder, some involving single cognitive deficits and some involving multiple cognitive deficits.

Within the literature on ASD, Happé (2003) presented the idea that different interacting casual factors and their associated neural abnormalities in multiple brain regions may map on to distinct abnormalities at the cognitive level. Happé suggested that instead of searching for genes of ASD as a whole, researchers should be searching for genes that predispose to different and distinct cognitive atypicalities in ASD. Therefore, it is important to know if ASD is characterised by a single or multiple cognitive atypicalities. Subsequently, Happé, Ronald, and Plomin (2006) proposed that the attempt to find a single cognitive account of ASD should be abandoned. Instead, different cognitive accounts that explain distinct symptoms of ASD should be sought (Happé, Ronald, et al., 2006), introducing the idea of a multiple cognitive deficit model of ASD. Accordingly, Pellicano, et al. (2006) examined the presence of multiple cognitive atypicalities in ASD. The results supported that not one but several cognitive deficits co-occur in ASD.

The fractionated theory of ASD suggests that there is no single cause at the genetic, neural or cognitive level for the diverse symptoms of ASD (Happé & Ronald, 2008). In addition, this theory suggests that the defining features of ASD are caused by different genes, associated with different brain regions, and related to different cognitive deficits. At the cognitive level, the fractionated theory suggests that multiple cognitive accounts may apply, instead of the traditional single cognitive deficit models of ASD, with each cognitive account explaining distinct symptoms of ASD. Therefore, the fractionated theory proposes a multiple cognitive deficit model for ASD, and Figure 1.4 illustrates two potential models within Mottron and Frith's (1995)

framework that this theory could imply. Figure 1.4b illustrates a strong version of the fractionated theory in which distinct causes at the genetic and neural levels relate to distinct deficits at the cognitive level, and these are associated with distinct symptoms of ASD at the behavioural level. Figure 1.4a demonstrates a weaker version of the fractionated theory in which different causes at the genetic and neural levels relate to deficits at the cognitive level. The different cognitive deficits relate to distinct symptoms, as in the strong version, but a single cognitive deficit can explain more than one symptom domain, and more than one cognitive deficit can explain a single symptom domain.

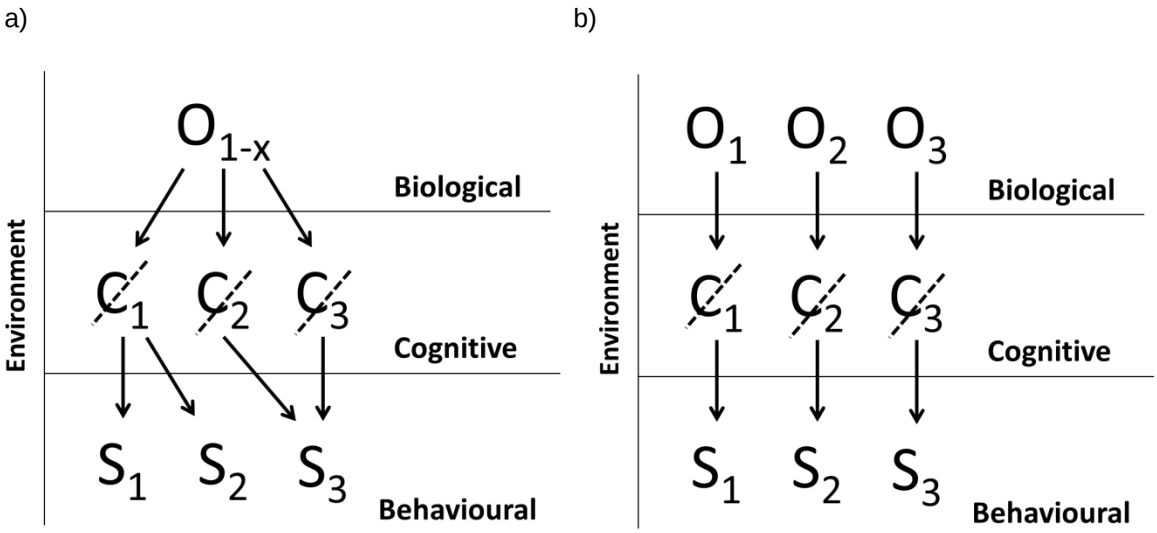


Figure 1.4. Representations of multiple cognitive deficit models (Happé & Ronald, 2008; Morton & Frith, 1995; Pennington, 2006). a) weak, and b) strong versions of the fractionated theory model (Happé & Ronald, 2008)

Notes: Arrows represent a causal relationship between levels. A horizontal line is used to separate levels. Hypothesised origins, O, represent genetic and brain abnormalities. The struck out C represents a cognitive domain that is found in normal development but is deficient/absent in ASD.

1.9 Summary

The purpose of this chapter was to provide an overview of ASD. A description of how the disorder was historically defined and how it is currently classified at the behavioural level was provided. The causes of the disorder at the genetic, neural, and cognitive levels were also considered. Particular focus was given to three cognitive theories of ASD; theory of mind deficit,

executive function deficit and weak central coherence. These three cognitive theories will be the primary focus of this thesis. The chapter also discussed the history, empirical evidence and the neural basis for these cognitive theories, and the challenges made against these cognitive theories.

The notion of single and multiple cognitive models was also introduced. Overall, the issue of a single versus a multiple cognitive deficit model for ASD is not resolved. However, it is unlikely that any single cognitive deficit is necessary and sufficient to cause ASD. A move to multiple cognitive deficit models of ASD is therefore warranted (Happé, Ronald, et al., 2006). The fractionated theory of ASD was briefly introduced, and will also be a primary focus of this thesis. Chapter 2 presents a review of the fractionation of ASD at the cognitive level, highlighting the predictions that the theory posits and the evidence for and against these predictions.

Chapter 2 Exploring the 'Fractionation' of Autism at the Cognitive Level

This chapter is adapted from the published article:

Brunsdon, V. E. A., & Happé, F. (2014). Exploring the 'fractionation' of autism at the cognitive level. *Autism, 18*(1), 17-30.

Austim is defined by difficulties across a range of areas; social and communication difficulties and restricted and repetitive behaviours and interests. Chapter 1 provided an overview to ASD. The fractionated triad theory suggests that the triad of symptoms in ASD cannot be explained by a single cause at the genetic, neural, or cognitive level (Happé & Ronald, 2008). The present chapter reviews the evidence for a 'fractionable' autism triad at the cognitive level, highlighting questions for future research.

2.1 Introduction

Autism has for many years been diagnosed on the basis of the characteristic 'triad' of impairments; social deficits, communicative impairments, and restricted and repetitive behaviours and interests (RRBIs) (World Health Organisation, 1992). Although the latest edition of DSM-5 (American Psychiatric Association, 2013) collapses social and communication symptoms into one domain (further discussed below), deficits across the three areas of the triad are still required for a diagnosis of 'Autism Spectrum Disorder'. Wing and Gould (1979) introduced the concept of the triad of impairments after finding that children with social impairments often exhibited communication deficits and impoverished imaginative play, with repetitive stereotyped behaviour.

Based on Wing and Gould's epidemiological data, it has long been assumed that the behavioural symptoms of ASD have common causes at the genetic, cognitive, and neural levels. However, Wing and Gould (1979) themselves noted that some children presented with only certain aspects of the triad. More recently it has been found that 10% of children in the general population present with just one impairment (defined as scoring in the most impaired 5%) without co-occurring deficits in other parts of the triad (Ronald et al., 2006) and modest-to-low phenotypic correlations between triad features have been reported in individuals with ASD

(Dworzynski, Happe, Bolton, & Ronald, 2009), and trait-wise in general population samples (Ronald, Happé, Price, Baron-Cohen, & Plomin, 2006). These findings have been taken to suggest that the triad of impairments is separable at the behavioural level, although this has been a matter of some debate. Work by Constantino and colleagues, for example, has suggested a single factor is sufficient to explain variation on the Social Responsiveness Scale (e.g., Constantino et al., 2004). However, more recent work by this group has supported a two factor solution, distinguishing social and communicative symptoms from rigid and repetitive behaviour (e.g., Frazier et al., 2012). In addition, twin studies have uncovered the relatively independent heritability of each of the three impairments of the triad (Robinson et al., 2012; Ronald et al., 2006; Ronald, Happé, Price, et al., 2006; Ronald, Larsson, Anckarsater, & Lichtenstein, 2011), suggesting that largely non-overlapping genes influence each part of the triad. These observations have led to the proposal of the 'fractionable' autism triad, a theory in which the social and non-social symptoms of ASD are suggested to have distinct causes at the genetic, neural, cognitive, and behavioural levels (Happé & Ronald, 2008; Happé, Ronald, et al., 2006). The purpose of the current chapter is to examine the proposal that autism is 'fractionable' at the cognitive level.

A range of cognitive accounts have been proposed to explain the symptoms of ASD and were discussed in Chapter 1. These theories posit either a primary deficit in the social domain (e.g., theory of mind, emotion processing, social motivation/reward) or in the non-social domain (e.g., executive dysfunction, weak central coherence, reduced top-down modulation). However, it is questionable whether any of these theories can account for the full triad of diagnostic features of ASD, let alone the associated features such as raised incidence of talents and uneven cognitive profile. For example, the theory of mind deficit hypothesis provides a good explanation for the social and communication impairments in ASD, but struggles to explain the non-social domain of ASD, such as RRBIs, motor problems, sensory abnormalities and savant skills. Conversely, non-social cognitive accounts of ASD provide a good explanation for the non-social aspects of ASD. For example, executive dysfunction in ASD may underlie RRBIs due to a failure to generate new behaviours or shift set. Additionally, a detail-focused cognitive style may account for 'insistence on sameness', narrow special interests and high rates of talent in ASD. Neither account, however, explains the specific pattern of intact and impaired social cognition (see Frith & Frith, 2010, for review). Consequently, Happé, Ronald, et al. (2006) proposed that

multiple cognitive accounts may apply, each explaining different parts of the ASD triad. This proposal makes a number of predictions (e.g. no one cognitive characteristic of ASD need be specific to ASD), but here we will focus on just two; (1) that performance on social and non-social cognitive tasks should be relatively unrelated, and (2) that specific cognitive tests should relate differentially to distinct aspects of the triad of symptoms in ASD.

This chapter reviews the evidence that cognitive functions are fractioned in ASD. First, the relative independence of cognitive functions will be explored. Second, published studies addressing the relation between cognitive tasks and symptoms in ASD will be summarised. Finally, a multiple cognitive deficit account of ASD, incorporating several cognitive functions, will be suggested to provide a better explanation for the complete profile of ASD.

2.2 Prediction (1): Relationship among Putative Cognitive Characteristics of ASD

While by no means the only cognitive theories of ASD, the 'theory of mind' (for review, see Frith, Morton, & Leslie, 1991), 'Executive dysfunction' (Hill, 2004) and 'weak coherence' (Happé & Booth, 2008; Happé & Frith, 2006) accounts are of sufficiently long-standing to have been examined empirically in relation to one another (introduced in Chapter 1). The fractionated triad account proposed that these three cognitive deficits/styles may be relatively independent and underlie different impairments in ASD (Happé & Ronald, 2008). What is the state of the empirical evidence to date?

2.2.1 Theory of Mind (ToM) and Executive Function (EF)

In contrast to the prediction that cognitive deficits are independent, a link between theory of mind and executive function in ASD has been reported. Studies with children with ASD have reported positive correlations between false-belief tasks testing ToM and tasks measuring various aspects of EF, including the Luria Hand Game (Bigham, 2010), the Windows task (Russell, et al., 1991), the NEPSY Knock-Tap task (no correlations with 4 other EF tasks; (Joseph & Tager-Flusberg, 2004), the Dimensional Change Card Sort task (Colvert, Custance, & Swettenham, 2002; Zelazo, Jacques, Burack, & Frye, 2002), the Wisconsin Card Sort Task, and the Tower of Hanoi (Ozonoff, et al., 1991). Ozonoff, et al. (1991) found that performance on

tasks measuring ToM and EF were related in ASD when controlling for IQ, although this correlation was not found in the control group. However, the ASD group exhibited a universal deficit in EF that was not apparent for ToM. Ozonoff et al.'s conclusion was that executive dysfunction is primary in ASD and is dissociable from ToM deficits, as the two deficits did not always co-occur. In contrast, Harris et al. (2008) reported that individuals with ASD who performed poorly on ToM performed poorly on EF tasks, and vice versa. In addition, Pellicano (2007) reported a significant correlation in an ASD group between a ToM composite and several components of EF (planning, set-shifting, and inhibition), independent of age and IQ. Furthermore, and contrary to Ozonoff et al's original finding, EF and ToM were dissociable in one direction only; impaired ToM with intact EF.

Pellicano's (2007) findings offer insight into a possible developmental relation between ToM and EF in ASD. Russell (1996; 1997) suggested that EF is crucial for the development of ToM and that deficits in EF may lead to a failure to develop mental state understanding in ASD. This has been supported in a recent study in which EF (shifting and planning) contributed significantly to ToM in young children with ASD (Kimhi, Shoam-Kugelmas, Ben-Artzi, Ben-Moshe, & Bauminger-Zviely, 2014). In addition, Pellicano's (2007) results showed that competent EF could be seen without ToM understanding. Examining the same cohort 3 years later, Pellicano (2010a) found that EF was longitudinally predictive of children's ToM test performance. A relation in the opposite direction was not found. Pellicano's work suggests that EF may be a prerequisite for ToM development and may also be critical in determining the developmental trajectory of children's ToM.

These findings do not support the fractionated theory of ASD, which predicts that the distinct cognitive impairments should be independent from each other. However, a number of points should be noted. First, correlational data do not speak directly to causation (Rutter, 2007), and two measures may show a relation due to, for example, general maturational factors at key developmental stages without any direct causal link. Second, cognitive tests are rarely 'process pure', and there is an important distinction to be made between correlations due to shared task demands, and correlations due to related underlying processes. For example, some ToM tasks (notably standard false-belief test) require *inhibition* of response based on own belief, and may therefore tap some aspects of EF as well as mental state attribution. Some EF tasks may also involve social elements; the Luria Hand Game (cited by Pellicano, 2007 as tapping inhibitory

control) may also tap the participant's ability to infer the experimenter's intentions so that the participant can produce the opposite action to the experimenter. Ozonoff (1995) showed that performance on a computerised version of the Wisconsin Card Sort Task showed less impairment in ASD than the traditional experimenter-presented version, again suggesting a possible social element to at least some standard EF tests. More recently however Williams and Jarrold (2013), using a more closely controlled experimental design, failed to find poorer performance on experimenter-administered planning and set-shifting tasks compared to computer versions of the same tasks in an ASD group.

White (2013) has recently proposed, in place of executive dysfunction accounts of ASD, a 'Triple I impairment'; impairment in 'Inferring Implicit Information'. White suggests that impairments on EF tasks are not in fact due to core executive dysfunction but instead secondary to mentalising difficulties, i.e., those with ASD have difficulties forming an explicit understanding of the experimenter's expectations of the task, resulting in irregular behaviour and performance on only those EF (and other) tasks where inferring this information is essential. It may also be hypothesised that problems in reflecting on *own* mental states (part of the ToM impairment in ASD; Williams & Happé, 2009) may have secondary consequences for EF: for example, difficulties in imaginatively rehearsing possible future activities may lead to impaired planning. While Williams and Jarrold (2013) study disconfirmed one prediction made by the Triple I hypothesis (better ASD performance on EF tasks when computer- versus experimenter-administered), the authors maintain that ToM and EF may be indirectly linked via developmental effects of ToM on communication and subsequent inner speech.

2.2.2 Central Coherence (CC) and ToM

The relation between central coherence and cognitive deficits in ASD has been less widely studied. Some studies have found no links between tasks measuring central coherence (CC) and ToM (Happé, 1997; Pellicano, et al., 2006). A local processing bias and poor global processing have been observed in children with ASD, regardless of whether they pass or fail ToM tasks (Happé, 1994a, 1997). Burnette et al. (2005) found a link between verbal measures of CC and ToM ability but this was no longer significant once IQ was taken into account. A similar pattern of results was noted by Pellicano, et al. (2006) who found that correlations between performance in ToM and weak CC measures disappeared once age, verbal ability, and

nonverbal ability were accounted for. Only one study has described a relation between individual differences in ToM and weak CC task performance in ASD (Jarrold, Butler, Cottington, & Jimenez, 2000). These authors concluded that a ToM deficit may be the result of an inability to take a global view of social situations and a weak drive to integrate social information. It should, perhaps, be noted that Happé and Booth (2008) have suggested that weak CC may itself reflect two separable components that are often confounded in tests; increased local processing and decreased global processing. This raises the possibility that, for example, superior eye for detail is unrelated to ToM, but that reduced integration of information in context may have a detrimental impact on understanding social situations and accurately attributing mental states.

There are a number of other theoretical accounts related to weak coherence, that posit only superior local processing, including Mottron et al.'s (2006) 'enhanced perceptual functioning' theory and Baron-Cohen's 'empathising-systemising' hypothesis (Baron-Cohen, 2009). The latter is relevant to the present discussion because systemising (the drive to discover and understand regular systems) is set in contrast to 'empathising' (understanding of social and emotional signals). In discussion of his model, Baron-Cohen typically portrays these social and non-social traits as orthogonal and independent. Though work from his lab on the effects of foetal testosterone suggests inverse effects on social-communicative functioning and visuo-spatial and repetitive ASD traits (Auyeung, Taylor, Hackett, & Baron-Cohen, 2010). However, the correlation between performance on tests of empathising (e.g. Reading the Mind in the Eyes) and systemising (e.g. folk physics) has not been widely assessed in an ASD sample; Baron-Cohen, et al. (2001) did report a significant negative correlation in a small sample of boys with Asperger syndrome.

2.2.3 CC and EF

Lastly, executive dysfunction and weak coherence appear to be dissociable (Booth, et al., 2003; Pellicano, 2010b; Pellicano, et al., 2006). Pellicano, et al. (2006) found that good performance on CC measures was related to better performance on EF tasks in an ASD group, but that correlations were not significant once age and ability were co-varied, perhaps in part because the CC measures used (e.g. Pattern Construction Task) tapped visuo-spatial ability along with style. In addition, Booth, et al. (2003) compared boys with ASD and those with ADHD on a

drawing task examining both cognitive processing style and planning ability. Only boys with ASD were more detail-focussed than controls, but both ASD and ADHD groups showed planning impairments. Furthermore, poor planning ability did not predict a detail-focussed cognitive style. Booth and Happé (2010) also report results from a verbal test of coherence in the same ASD and ADHD groups. Here again, only ASD boys were characterised by detail-focus (making more local sentence completions), while both ASD and ADHD groups showed response selection deficits on a Go No-Go task, and performance on the two tests was not significantly correlated. Research to date therefore suggests that weak coherence is independent of executive dysfunction, in line with the proposals of the fractionable triad account of ASD.

Finally, Pellicano (2010a; 2010b) conducted the first prospective study to investigate the development of multiple cognitive atypicalities in ASD over a three year period. Group differences were reported; children with ASD showed difficulties in false-belief understanding, higher-order planning and cognitive flexibility at ages 4-7 years and 7-10 years old relative to typically-developing controls. Principal components analysis at time 1 yielded four factors, with ToM, CC and EF measures falling on separate factors – perhaps supporting in part a fractionable triad view. At time 2, however, only two factors emerged, with the ToM and EF tasks loading together and only the CC measures remaining distinct. Examining predictors of change over time, Pellicano found that change in ToM showed independent influence from EF and CC performance, while change in EF was not predicted by ToM or CC (over and above time 1 EF and general ability measures), nor was change in CC performance significantly predicted by ToM or EF measures. Thus the pattern of inter-relations was partly supportive of and partly counter to a fractionable triad view: while EF and CC emerged as relatively distinct, ToM and EF showed a significant concurrent (at time 2) and developmental relation. The relation between ToM and EF has also been much discussed and researched in the literature on typical development (e.g., Hughes & Ensor, 2007) and acquired neurological damage (e.g., Aboulafia-Brakha, Christe, Martory, & Annoni, 2011), with evidence of strong associations between task performance in the two domains. However, given the specific focus on ASD in this thesis, further discussion of this work is beyond the scope of the current chapter.

2.3 Prediction (2): Relations Between Cognitive Accounts and Behavioural Symptoms

The fractionated triad theory of autism suggests that different cognitive functions may underlie the distinct symptom domains of ASD (Happé & Ronald, 2008). This predicts that performance on, for example, ToM tests should relate most strongly to social-communicative symptoms, while executive dysfunction tests may correlate best with non-social repetitive behaviour, and CC measures may relate specifically to uneven cognitive profile, talents and narrow interests. However, surprisingly few studies have investigated whether different cognitive functions are differentially related to distinct parts of the ASD triad of impairments. Of course, the prediction of differential cognition-behaviour links rests on an assumption that significant correlations can be found between any cognitive tasks and everyday behaviours, symptoms or traits. Studies examining these links, and specifically those relevant to the differential links prediction of the fractionable triad hypothesis, are summarised in Table 2.1 and briefly reviewed below.

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Theory of Mind						
Ames and White (2011)	55 ASD (9 autism, 30 AS, 16 ASD/PDD-NOS); 48M, 7F, CA 10, VIQ 105, PIQ 94	Prior clinician diagnosis	/	Theory of Mind Battery, Hayling Sentence Completion Test (to test inhibitory control)	Developmental, Dimensional and Diagnostic Interview (3Di)	Low ASD-social impairment group > high ASD-social impairment group on inhibitory control & ToM tasks (d= 0.55). ToM predicts social interaction in ASD (R^2=.08), but not in ADHD group.
Bennett et al. (2013)	Time 1: 68 HFA; CA 7, IQ>68, PIQ 86 Time 2: 39 HFA; CA 15 Time 3: 35 HFA; 31M, 4F, CA 17	DSM-III-R criteria	Time 1 language	Time 2: Reading the Mind in the Eyes test	Vineland Adaptive Behaviour Scales (VABS)	Time 2 ToM predicts time 3 VABS Communication, controlling for language, but not Socialization.
Frith, et al. (1994)	24 autism; 17M, 7F, CA 15, MA 7, VIQ 52 15 TD; 5M, 10F, CA 4, MA 4, VIQ 93 11 MLD; 7M, 4F, CA 9, MA 5, VIQ 60	DSM-III-R criteria	/	2 FB tasks (Groups divided into passers & failers).	VABS	ASD ToM-passers > ToM-failers on VABS Communication (d=0.63) & Socialization (d=0.54) domain scores.

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Golan, Sinai-Gavrilov, and Baron-Cohen (2015)	30 ASD; 29M, 1F, CA 10, VIQ 113, PIQ 111 25 TD; 24M 1F, CA 10, VIQ 114, PIQ 115	Prior clinician diagnosis	Gender, age, VIQ, PIQ	Cambridge Mindreading Face-Voice Battery for Children (CAM-C), Reading the Mind in the Eyes test	Childhood Autism Spectrum Test (CAST)	CAM-C scores correlated with CAST (r = -.48/-.54)
Lerner, Hutchins, and Prelock (2011)	30 ASD; 24M, 6F, CA 14	Prior clinician diagnosis plus SCQ & SRS	/	Theory of Mind Inventory	Social Communication Questionnaire (SCQ), Social Skills Rating System – Parent, Social Responsiveness Scale (SRS)	ToM scores X parent reported social skills correlated (r=.61), ToM scores X autism-related social impairment negatively correlated (SCQ r= -.55, SRS r= -.75) Higher social skills & fewer autistic symptoms predicts ToM scores (R^2=.66).
Loth, Happé, and Gomez (2010)	20 ASD (HFA or AS); all M, CA 12, FIQ 108, VIQ 107, PIQ 107 18 TD; all M, CA 11, FIQ 109, VIQ 109, PIQ 112	Prior clinical diagnosis	CA, VIQ, PIQ	ToM: FB task, Strange Stories CC: Embedded Figures Test (EFT), Block Design, Sentence Completion Task	CAST	No correlation between ToM or CC tasks & ASD symptoms (r's< .27).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Shimoni, Weizman, Yoran, and Raviv (2012)	25 ASD child; CA 13 25 ASD child's mother; CA 42 25 ASD child's father; CA 47 28 TD child; CA 14 28 TD child's mother; CA 43 28 TD child's father; 46	ADOS-G	Age, education & income of parents	ToM: Social Attribution task	Children: ADOS-G, ADI-R, VABS, Parents: ADI-R, VABS-Expanded Edition	Pertinence index positively correlated with ADI-R social interaction (r=.27) & communication deficits (r=.39). Salience index negatively correlated with ADI-R (r=-.35) & communication deficits (r=.34). ToM Affective & Salience indices correlated with ADOS-G (Stereotypic and Limited interest items) (r=.51).
White, et al. (2009)	45 ASD (8 autism, 25 AS, 12 ASD); 41M, 4F, CA 9, VIQ 111, PIQ 98 27 TD; 21M, 6F, CA 9, VIQ 115, PIQ 103	Prior diagnosis, confirmed with 3Di	Matched gender, CA, VIQ, PIQ	Standard ToM battery; 11 FB tasks & Penny-Hiding task, Strange Stories	3Di	ASD children with poor ToM had more severe social (d=0.83) & communication (d=0.69) symptoms, but not repetitive behaviours.
Executive Function						
Akbar, Loomis, and	62 ASD; 47M, 15F, CA 9, FIQ 80	ADI-R, ADOS-G	/	Delis-Kaplan Executive Function System,	ADI-R, ADOS-G	Symptom severity does not predict inhibition, working memory or organisation

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Paul (2013)				Developmental Neuropsychological Assessment, Behaviour Rating Inventory of Executive Functioning (BRIEF)		score. Both PIQ & severity of ASD symptoms predicts EF shift score (R^2=.33).
Bishop and Norbury (2005)	14 HFA; PIQ 107 17 SLI; PIQ 99 25 PLI; PIQ 105 18 TD; PIQ 111	SCQ & ADOS-G	PIQ	Two subtests from Test of Everyday Attention for Children (to measure inhibition)	ADOS, SCQ, Children's Communication Checklist	No correlation between inhibition & symptom measures of ASD (r's< .14)
Boyd, McBee, Holtzclaw, Baranek, and Bodfish (2009)	61 HFA (31 autism, 22 AS, 5 PDD-NOS); CA 10, IQ 100 64 TD; CA 12, IQ 111	DSM-IV criteria, ADI-R, SCQ	/	BRIEF	Repetitive Behaviour Scale- Revised (RBS-R), Sensory Questionnaire	Behaviour regulation correlated with repetitive behaviour (r=.43), not sensory impairments (r=.03). A diagnosis of ASD, lower age, higher scores on Sensory Questionnaire & BRIEF Behaviour Regulation predicts RBS-R total score (R^2=.86).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
D'Cruz et al. (2013)	41 ASD (22 autism, 12 PDD-NOS, 7 AS); 34M, 7F, CA 15, FIQ 104, VIQ 102, PIQ 105 37 TD; 30M, 7F, CA 18, FIQ 109, VIQ 109, PIQ 107	DSM-IV-TR, ADOS, ADI-R	CA, gender, IQ	Probabilistic Reversal Learning Task	ADI-R, RBS-R	Positive correlation between poor flexible behaviour & RBS-R total score (r=.34), ADI RRBI score (r=.37) and stereotyped, repetitive, or idiosyncratic behaviour (ADI-R B3 subscale; r=.38).
Dichter, Lam, Turner-Brown, Holtzclaw, and Bodfish (2009)	50 ASD; CA 10 IQ 102 42 TD; CA 11 IQ 112	DSM-IV criteria, ADI-R , SRS	CA	Generavity tasks: Animals Fluency Task, The Use of Objects task	ADI-R, SCQ, SRS, RBS-R, Children's Communication Checklist	Only correlations between communication impairments & animal fluency task scores (r=.42-.46). No correlation between generativity & repetitive behaviours (r< .30).
Faja and Dawson (2014)	23 ASD; 18M 5F, CA 6.9, IQ 102 20 TD; 15M, 5F, CA 6.7, IQ 108	ADI-R, ADOS	Age, gender, IQ	Dimensional Change Card Sort (DCCS), Children's Memory Scale Numbers	ADI-R, ADOS, Social Skills Rating System (SSRS), RBS-R	ASD who passed DCCS had better social communication skills (SSRS; η=.27). No differences between passers/failers on DCCS for ASD symptoms (ADOS, ADI, RBS-R)

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Gilotty, Kenworthy, Sirian, Black, and Wagner (2002)	35 ASD (HFA or autism); 30M, 5F, CA 10, IQ 104	DSM-IV criteria	/	BRIEF	VABS	BRIEF Initiate & Working Memory subscales negatively correlated with Communication (r=-.48; r=-.52) and Socialization domains of VABS (r=-. 64; r=-.57).
Kenworthy, Black, Harrison, della Rosa, and Wallace (2009)	89 ASD (34 autism, 32 AS, 23 PDD-NOS); CA 10, VA 10	DSM-IV criteria, ADI-R, ADOS	/	BRIEF, Test of Everyday Attention for Children, Tower of London, Semantic Fluency	ADI, ADOS	EF tasks predict communication symptoms (semantic fluency: β=-.63; BRIEF: β=.30), social interaction symptoms (divided attention & working memory: β=-.44; semantic fluency: β=-.60) and RRBIs (BRIEF: β=.38), after accounting for VA & age.
LeMonda, Holtzer, and Goldman (2012)	22 ASD; 5F, 17M, CA 8, PIQ 98 22 DLD; 5F, 17M, CA 8, PIQ 99	DSM-III-IR criteria, Wing Autistic Disorder Interview Checklist	CA, gender, PIQ, parent education.	Wisconsin Card Sorting Task, Mazes subtest of Wechsler Intelligence Scale for Children, Revised Edition, Matrices subtest of Stanford-Binet Fourth Edition	Stereotypies measure: 30-min coded video of semi-structured play	EF tasks predict motor stereotypies (R^2=.33). Lower EF scores predict higher frequencies & longer duration of stereotypies in ASD group only (β≥-.48 ≤-.26).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Lopez, Lincoln, Ozonoff, and Lai (2005)	17 ASD; CA 29 17 TD; CA 29	ADI-R, ADOS-G, Gilliam Autism Rating Scale	CA	Delis-Kaplin Executive Function Scale, Wisconsin Card Sorting Task	ADOS, ADI-R, Gillam Autism Rating Scale, Aberrant Behavior Checklist-Community	Cognitive flexibility, working memory, & response inhibition correlated with RRBIs (r=.63; r=-.56; r=.58, respectively). Planning & fluency not correlated with RRBIs (r=-.09; r=-.45, respectively). Together, cognitive flexibility, working memory, and response inhibition accounted for a significant proportion of variance in RRBIs (R^2=.52).
McEvoy, Rogers, and Pennington (1993)	17 autism; 10M, 7F, CA 5, NVA 12, VA 14 13 DD; CA 4, NVA 12 16 TD; 10M, 6F, CA 3, VA 20	DSM-III-R criteria, Childhood Autism Rating Scale	Autism & DD: NVA, CA Autism & TD: VA	Piagetian AB Error Task, Delayed Response Task, Spatial Reversal Task, Alternation Task	Early Social Communication Scales	Social interaction & EF correlated (r=-.44), in part due to social interaction and joint attention being correlated (r=.42).
Miller, Ragozzino, Cook, Sweeney,	60 ASD; 50M, 10F, CA 15, VIQ 100, NVIQ 101 55 TD; 41M, 14F, CA	ADI-R, ADOS, DSM-IV criteria	Age, gender, NVIQ	Penn Condition Exclusion Test	ADI-R, ADOS	Perseverative errors correlated with ADOS RRBI scores (r = .31), not related with social or communication scores on ADI or ADOS

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
and Mosconi (2015)	16, VIQ 110, NVIQ 107					
Mosconi et al. (2009)	18 ASD (13 autism, 5 AS); 14M, 4F, CA 18, VIQ 110, PIQ 107, FIQ 109 15 TD; 11M, 4F, CA 20, VIQ 110, PIQ 107, FIQ 110	DSM-IV criteria, ADI-R, ADOS-G	CA, IQ	Visually-guided Saccade Task	ADI-R	Impairments in inhibitory control & higher-order RRBIs positively correlated (r=.65), after controlling for age (partial r=.73).
Reed, Watts, and Truzoli (2013)	15 ASD; CA 8, PIQ 71, MA 6 15 TD; CA 7	DSM-IV, plus Gilliam Autism Rating Scale	Matched ASD MA to TD CA	Card Sort Task	Gilliam Autism Rating Scale	Perseverative errors correlated to stereotyped behaviours (r=.69). Perseverative errors not correlated to communication difficulties or social interactions (r's< .26).
Teunisse, Cools, van Spaendonck, Aerts, and Berger	35 HFA; 26M, 9F, CA 19, VIQ 91	DSM-IV criteria	/	Card Sorting Tests, CANTAB Intradimensional/Extradimensional shift (ID/ED), Switch-in-series	Checklist of 12 DSM-IV diagnostic criteria, Wechsler Adult Intelligence Scale - Picture Arrangement,	No correlations between EF tasks & social measures (social IQ r=-.31, social competence r=-.03, ASD symptoms r=.22).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
(2001)					VABS Socialization Domain	
van den Bergh, Scheeren, Begeer, Koot, and Geurts (2014)	118 ASD; 102M, 16F, CA 13, IQ 105	Prior clinical diagnosis (DSM-IV-TR), SRS	/	BRIEF	ADOS	No correlations between BRIEF subscales and ADOS. Autism severity did not add uniquely to variance of inhibition scale (all other subscale regression models were non-significant)
Yerys et al. (2009)	42 ASD (35 HFA, 7 PDD-NOS); 33M, 9F, CA 10, FIQ 112 84 TD; 65M, 19F, CA 10, FIQ 113	DSM-IV-TR criteria ADOS-G, ADI-R	/	ID/ED	ADI-R	ID/ED & RRBI domain of ADI-R correlated (r= .43, FIQ partialled out). ID/ED & social or communication domain scores not correlated (social symptoms r=.19; communication symptoms r=.20).
Zandt, Prior, and Kyrios (2009)	19 ASD (15 AS, 2 autism, 1 PDD-NOS; 16M, 3F, CA 11, VIQ 96, PIQ 95	DSM-IV-TR	CA, VIQ, PIQ	Verbal Fluency Task, Concept Generation Task – Child Version, Rey Figure, Walk Don't Walk Task,	Repetitive Behaviour Questionnaire, Children's Yale-Brown Obsessive Compulsive	Impairment in EF related to higher rates of RRBIs (r= -.54).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
	17 OCD; 8M, 9F, CA 12, VIQ 94, PIQ 96 18 TD; 6M, 12F, CA 12, VIQ 95, PIQ 103			BRIEF	Scale	
Central Coherence						
Burnette, et al. (2005)	Time 1: 31 HFA; 26M, 5F, CA11 16 TD; CA 11 17 LD; Time 2 (15-19 months): 23 HFA; 19M 4F, VIQ 110, PIQ 110 20 TD (12 TD + 6 LD +2 new LD); 15M, 5F, CA 11, VIQ 117, PIQ 117	DSM-IV	VIQ, PIQ	Block Design, Differential Ability Scales - Pattern Construction, EFT, Homograph Task	High-Functioning Autism Spectrum Screening Questionnaire, Australian Scale for Asperger Syndrome	No correlations between CC tasks & ASD symptoms (no statistics stated).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Chen, Rodgers, and McConachie (2009)	29 ASD; 26M, 3F, CA 12, IQ 114	Clinical diagnosis, ADOS, SCQ	/	EFT	Childhood Routines Inventory, Short Sensory Profile	Degree of RRBIs (r= -.39), but not sensory abnormalities (r= -.02), predict completion time on the EFT.
Drake, Redash, Coleman, Haimson, and Winner (2010)	27 TD; 9M, 18F, CA 10	/	/	Block Design, EFT, Copying Task	Childhood Autism Spectrum Test	Performance on CC tasks not related to RRBIs (r's< .27).
Loth, et al. (2010)	20 ASD (HFA or AS); all M, CA 12, FIQ 108, VIQ 107, PIQ 107 18 TD; all M, CA 11, FIQ 109, VIQ 109, PIQ 112	Prior clinical diagnosis	CA, VIQ, PIQ	EFT, Block Design, Sentence Completion Task	Childhood Autism Spectrum Test	No correlation between CC tasks & ASD symptoms (r's< .27).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Morgan, Maybery, and Durkin (2003)	21 ASD (19 autism, 2 PDD-NOS); 19M, 2F, CA 5, MA 3, PIQ 95, VIQ 77 21 TD; 16M, 5F, CA 5, MA 5, PIQ 105, VIQ 101	DSM-IV criteria	Gender, CA, PIQ	Preschool EFT, Differential Ability Scales - Pattern Construction	ADI-R, ADOS	CC predicts ASD group membership (d=1.86).
Olu-Lafe, Liederman, and Tager-Flusberg (2014)	21 ASD (all M), CA 20, IQ 105 20 TD (all M), CA 20, IQ 102	Prior clinical diagnosis (DSM-IV-TR)	Age, IQ	Silhouette-to-Shape Matching task, Shape-Integration task	ADOS, SRS	No correlations between task performance and social symptom severity. RT difference score and SRS-Social Motivation subscale score correlated (r = .51).
Russell-Smith, Maybery, Bayliss, and Sng (2012)	80 TD; CA 19, 56F	/	Age & gender	EFT (group divided by AQ 'social skills' & 'details/patterns' (either high or low)	Autism Spectrum Quotient	EFT scores: High social difficulty>Low social difficulty (d=.59). High detail/patterns=low detail/patterns (d=.17).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
South, Ozonoff, and McMahon (2007)	19 ASD; 14M, 5F, CA 15, VIQ 115, PIQ 111, FIQ 114 18 TD; 11M, 7F, VIQ 112, PIQ 113, FIQ 112	DSM-IV criteria, ADI-R, ADOS-G	CA, VIQ, PIQ, FIQ	EFT, Gestalt closure test	ADOS, ADI-R, Repetitive Behaviour Interview, Yale Special Interests Interview	No correlations between CC tasks & RRBI measures (r's< .30).
Teunisse, et al. (2001)	35 HFA; 26M, 9F, CA 19, VIQ 91	DSM-IV criteria		Children's EFT, EFT, California Verbal Learning Test-Semantic and Serial Gradient, Visual Object and Space Perception Test - Object Recognition Tasks, Search-for-Difference Task	Checklist of 12 DSM-IV diagnostic criteria, Wechsler Adult Intelligence Scale - Picture Arrangement, VABS Socialization Domain	No correlations between CC tasks & social measures (social IQ r= .00, social competence r= .16, autistic symptoms r= .11).
White and Saldana (2011)	45 ASD; 41M, 4F, CA 9, VIQ 111, PIQ 98 27 TD; 21M, 6F, CA 9, VIQ 115, PIQ 103	Prior diagnosis (ICD-10), confirmed with 3Di	Gender, CA, VIQ, PIQ	Children's EFT	3Di	No correlations between EFT & ASD symptomatology (r<.22).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Multiple cognitive deficits						
Joseph and Tager-Flusberg (2004)	31 ASD (27 autism, 4 ASD); CA 9, VIQ 20, PIQ 23	DSM-IV criteria, ADI-R, ADOS	/	5 EF tasks; Word Span, Block Span, Day-Night, Knock-Tap, Tower	ADOS	ToM correlated with communication (r=-.64), but not social symptoms or RRBIs when non-verbal mental age & language controlled for (r's< .34). Language (R^2=.33), ToM ability (R^2=.28) and Tower score (R^2=.05) predicts communication symptoms. Neither ToM nor EF accounted for additional variance in social interaction or repetitive behaviour symptoms.
Pellicano, et al. (2006)	40 ASD (30 autism, 10 PDD-NOS); 35M, 5F, CA 5.6, VIQ 101, PIQ 114 40 TD; 31M, 9F, CA 5.4, VIQ 103, PIQ 113	DSM-IV criteria, confirmed with ADI-R. TD screened with SCQ	CA, VIQ, PIQ, gender	CC: EFT, Pattern-Construction task, Figure-Ground task, Developmental Test of Visual- Motor Integration ToM: 6 1st FB tasks, 2 2nd FB tasks. EF: Luria's Hand Game, Mazes task, ToL, Set-shifting task	ADI-R	All cognitive tasks failed to correlate with either ADI-R total or domain scores. EFT & social domain (at 4-5 years) negatively correlated (r=.41).

Table 2.1. Published studies assessing cognitive domains in relation to symptom type and severity in autism spectrum disorder

Reference	Participants (group means)	ASD Diagnosis	Control variables	Cognitive Tasks	Symptom Measures	Relevant Findings (with effect sizes)
Pellicano (2013)	Time 1 45 ASD; 40M, 5F, CA 5.6, VIQ 97, PIQ 113 45 TD; 37M, 8F, CA 5.4, VIQ 101, PIQ 116 Time 2 (3-years) 37 ASD; 33M, 4F, CA 8.4, VIQ 94, PIQ 104 31 TD; 25M, 6F, CA 8.2, VIQ 100, PIQ 107	DSM-IV criteria, time 1 with ADI-R, time 2 with ADOS-G	Age, VIQ, PIQ (at time 1)	Time 1: ToM: 2 first-order FB tasks, 1 second-order FB task EF: Teddy-bear set-shifting task, Luria's Hand Game, Mazes task CC: EFT, Pattern Construction task, Figure-Ground task	Time 2: ADOS-G, Repetitive Behaviour Questionnaire	ToM negatively correlated with social-communication (r=-.42). EF negatively correlated with social-communication and RRBIs (both r=.42). CC not correlated (r< .21). EF predicts symptom severity (ADOS; R^2=.16) and repetitive behaviours (R^2=.15).

Note: Cohen's d, Pearson's correlation coefficient r, and R^2 are reported to convey effect sizes. Small, medium, and large effects for d are considered as 0.2, 0.5, and 0.8, respectively, and for r are considered as 0.1, 0.3 and 0.5, respectively (Cohen, 1969). Small, medium, and large effects for R^2 are considered as 0.01, 0.09 and 0.25, respectively (Cohen, 1988). In the 'Participants' column, participant characteristics for ASD groups are reported first, followed by participant characteristics for any comparison groups. In order to group studies by cognitive domain, some papers appear more than once.

Key: β: standardised regression coefficient; 3di: Developmental, Dimensional and Diagnostic Interview; ADI: Autism Diagnostic Interview; ADOS: Autism Diagnostic Observation Schedule; AS: Asperger syndrome; ASD: autism spectrum disorder; BRIEF: Behaviour Rating Inventory of Executive Functioning; CA: chronological

age in years; CC: central coherence; CELF: Clinical Evaluation of Language Fundamentals; d: Cohen's d; DD: developmental delay; DSM: Diagnostic and Statistical Manual of Mental Disorders; EF: executive function; EFT: Embedded Figures test; F: females; FB: false-belief; FIQ: full-scale intelligence quotient; HFA: high-functioning autism; ID: intellectually disabled; ID/ED: Intradimensional/Extradimensional shift; M: males; MA: mental age in years, MLD: moderate learning difficulties; NVA: non-verbal ability; OCD: obsessive compulsive disorder; PDD-NOS: pervasive developmental disorder – not otherwise specified; PIQ: performance intelligence quotient; PLI: pragmatic language impairment; r: correlation coefficient; R^2: coefficient of determination; RBS: Repetitive Behaviour Scale – revised; RRBIs: restricted and repetitive behaviours and interests; SCQ: Social Communication Questionnaire; SLI: specific language impairment; SRS: Social Responsiveness Scale; TD: typically developing, ToM: theory of mind; VA: verbal ability; VABS: Vineland Adaptive Behaviour Scales; VIQ: verbal intelligence quotient

2.3.1 ToM and ASD Symptoms

Specific deficits in social cognition, specifically impaired ToM, are hypothesised to underlie the social and communicative symptoms that define ASD (see Tager-Flusberg, 1999). A number of studies have reported a relation between performance on ToM tasks and everyday social abilities in ASD. An early study by Frith, et al. (1994) found significantly better real-life social insight (e.g. ability to keep secrets, understand lies) in children with ASD who passed ToM tasks compared to those who failed. Four recent studies have supported and extended this finding. Lerner, et al. (2011) found that ToM ability was negatively correlated with ASD symptoms and social impairments and that fewer ASD symptoms significantly predicted higher ToM scores. Ames and White (2011) investigated the relation between ADHD-related behaviours in a sample of children with ASD and behavioural and cognitive impairments. Poorer performance on ToM measures was significantly related to social difficulties but not to ADHD-related behaviours. Shimoni, et al. (2012) found that performance on tasks measuring various aspects of ToM was related to social and communication impairments in ASD, as measured by the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Lecouteur, 1994). Finally, Bennett, et al. (2013) reported a significant association between ToM ability in late childhood with later communication skills in adolescence (when controlling for language ability in childhood).

However, not all studies have found a significant relation between performance on ToM measures and everyday social ability in ASD. For example, Loth and colleagues found no significant relation between symptoms of ASD and ToM ability in a group of boys with ASD (Loth, et al., 2010). In addition, Bennett, et al. (2013) found no significant associations between ToM ability in late childhood with later social skills in adolescence. Overall, previous findings favour a link between ToM and social skills in ASD, but further studies are necessary to understand the somewhat mixed findings.

2.3.2 EF and ASD Symptoms

Executive dysfunction has been hypothesised to explain the restricted and repetitive behaviours and interests (RRBIs) observed in individuals with ASD. Difficulties in inhibiting inappropriate behaviour, shifting set, and generating appropriate new behaviours, have been hypothesised to underlie RRBIs (Turner, 1997). Several previous studies have investigated RRBIs in ASD in relation to specific executive processes. Turner (1995) found RRBIs were most strongly linked

to generativity deficits (e.g., verbal fluency) in a sample of young people with ASD. Mosconi, et al. (2009) reported that impaired inhibition of prepotent responses was related to increased severity of higher-order repetitive behaviours (e.g. compulsions) in ASD. Furthermore, inhibitory control was unrelated to social and communication symptoms, or sensorimotor behaviours. The same pattern was found for the EF domain of set-shifting; Yerys, et al. (2009) reported a significant correlation between set-shifting difficulties and repetitive behaviour (but not social or communicative symptoms) in ASD. South, et al. (2007) also found support for a link between cognitive flexibility and repetitive behaviours in children with ASD. In addition, behavioural flexibility has been recently reported to be related to RRBI behaviours but not to social or communication symptoms, in both high- and low-functioning ASD (D'Cruz, et al., 2013; Reed, et al., 2013). Taking a more comprehensive view of EF, Lopez et al (2005) noted that some specific executive processes (cognitive flexibility, working memory, and response inhibition) were highly related to RRBIs, whereas other executive processes (planning and fluency) were not significantly correlated with RRBIs in adults with ASD.

Just as 'EF' is an umbrella term covering many dissociable components, the restricted and repetitive behaviours and interests (RRBIs) diagnostic of ASD are a varied set. For example, Szatmari et al. (2006) found that RRBIs, as measured by the ADI-R, loaded onto two factors; insistence on sameness versus repetitive sensory and motor behaviours. It may be important to distinguish which aspects of RRBIs are correlated with distinct domains of executive dysfunction. LeMonda, et al. (2012) measured various aspects of EF in children with ASD and developmental language disorders. Lower EF scores predicted higher incidences and longer durations of motor stereotypies (e.g., hand flapping, rocking) in ASD only, when controlling for age, gender and parental education. On the other hand, Boyd, et al. (2009) found that EF correlated with RRBIs but not with sensory abnormalities.

Not all studies have documented a significant relation between EF and RRBIs. Zandt, et al. (2009) assessed several executive processes and RRBIs in individuals with obsessive compulsive disorder and ASD. The only significant relation uncovered was between generativity and obsessions in the ASD group. Dichter, et al. (2009) also found no relation between generativity ability and severity of RRBIs, nor with subscales of higher- or lower-order repetitive behaviours. In contrast, they found that impaired generativity was related to communication impairments. In a different domain of EF, Bishop and Norbury (2005) did not find an association

between inhibition and any of the three symptoms domains of ASD. Failure to find a significant relation between executive processes and specific symptoms of ASD may in some cases reflect limited sample size and hence statistical power (e.g., Teunisse, et al., 2001). In addition, there is currently no single task or battery of tasks to cover comprehensively all aspects of EF, and different findings may reflect different task or domain selection (see, for example, White's division of EF tasks according to implicit ToM demands, discussed above).

While executive dysfunction has been hypothesised to explain RRBIs in ASD, it may also be relevant to everyday social interaction. Social interactions likely tax many aspects of EF, such as *initiation* of social approach, *flexibility* in social response, *attention* to social cues such as facial expressions, *inhibition* of socially inappropriate behaviour, and keeping social networks or different individuals' mental states in *working memory*. In support of this, a link between EF and social communication skills has been described in young children with ASD (McEvoy, et al., 1993). A more comprehensive study was undertaken by Kenworthy, et al. (2009) to investigate the link between EF and the three symptoms domains of ASD. A composite of scores from the ADI-R and the ADOS was used to characterise the three symptom domains and performance in multiple aspects of EF was examined. Correlation and regression analyses indicated that semantic fluency and divided attention were related to social symptoms, semantic fluency was related to communication symptoms, and cognitive flexibility was related to RRBIs, after accounting for verbal ability and age. This study shows the potential for the executive dysfunction account to expand beyond explaining RRBIs to include social and communication symptoms. The applicability of these results to everyday adaptive behaviour has been explored by Gilotty, et al. (2002); initiation of behaviour and working memory were found to be related to impairments in social interaction and communication. Thus, some specific elements of EF may have a special relation with social and communication impairments in ASD.

2.3.3 CC and ASD Symptoms

The weak central coherence theory of ASD, describing detail-focus and difficulty integrating information in context for meaning (Frith, 1989), was proposed to explain 'insistence on sameness', narrow interests, uneven cognitive profile, and perhaps sensory abnormalities and savant skills (Happé & Vital, 2009). However, as detailed below, studies that have investigated

the association between a detailed-processing style and the symptoms of ASD have produced mixed results.

Chen, et al. (2009) found a link between a detail-focused processing style in the visual domain and degree of repetitive behaviour in children with ASD. However, there was no relation between detail-focused processing and sensory processing abnormalities. They concluded that sensory processing is a lower-level process and so cannot be directly compared to performance on higher-level CC tasks. Loth, Gomez, and Happe (2008) used sensitivity to context-appropriateness in a change blindness paradigm to tap CC, and found a moderate but only marginally significant relation (r = -.49) between ADOS RRBI scores and differences in change detection as a function of context in an ASD sample. Other studies have found no relation between several measures of repetitive behaviours and CC measures in both children with ASD (South, et al., 2007) and typically-developing children (Drake, et al., 2010). In general, there is a surprising paucity of studies, considering the theoretical appeal of the weak CC account in explaining restricted and repetitive behaviours in ASD – perhaps reflecting the relative lack of research on non-social (compared to social/communicative) aspects of ASD.

Happé and Frith (2006) have specifically limited the explanatory scope of the weak CC account to the non-social features of ASD. However, detail-focus may also have interesting implications for social and communicative functioning in ASD (e.g., Noens & van Berckelaer-Onnes, 2005; Noens & van Berckelaer-Onnes, 2008). Social interactions involve the integration of discrete cues in context to understand social situations. For example, face-processing and (context-dependent) communication may involve the integration of local details (e.g., facial features) in context. An association between detailed-processing bias and social impairments in 'neurotypical' undergraduates has been reported (Russell-Smith, et al., 2012). However, weak coherence has been reported to be unrelated to several measures of social symptoms in ASD samples (Burnette, et al., 2005; Teunisse, et al., 2001). For example, Morgan, et al. (2003) found no relation between measures of CC and social or communicative skills (e.g., joint attention and pretend play) in children with ASD aged three to five years.

2.3.4 ToM, EF and CC in Relation to ASD Symptoms

Only a handful of studies have considered multiple cognitive deficits in relation to the behavioural symptoms of ASD. For example, amongst a sample of pupils receiving extra

support with learning, Best, Moffat, Power, Owens, and Johnstone (2008) found that ToM, weak CC, and EF, all contributed significantly and independently to the prediction of behavioural indicators of ASD (measured by the Social Communication Questionnaire). Only three studies have specifically investigated the relation between test performance in all these cognitive tasks and the symptoms domains in individuals with ASD. In Joseph and Tager-Flusberg (2004) study, the ADOS was used to measure symptom severity in children with ASD, and ToM and EF tests were administered. Limited relations were found between the two cognitive tasks and symptom severity in ASD, and relations could be largely accounted for by language ability. However, ToM ability and higher-level EF were significantly related to the severity of communication symptoms in ASD, while reciprocal social interaction and RRBIs were relatively independent. Additionally, in Pellicano, et al.'s (2006) study, children with ASD completed the ADI-R as a measure of symptom severity, and were administered a similar battery of tasks to measure CC, ToM and EF. Contrary to Joseph and Tager-Flusberg's (2004) findings and their own predictions, the three cognitive profiles failed to correlate with any of the three symptom domains of ASD.

Pellicano (2013) examined whether early cognitive skills could predict later behavioural symptoms of ASD as measured by the ADOS and Repetitive Behaviour Questionnaire at a 3-year follow-up. ToM was negatively associated with social-communication skills and EF was strongly associated with both social-communication skills and repetitive behaviours. Specifically, early EF, not ToM ability, predicted the degree of social-communication impairment and repetitive behaviours, thus elucidating the important role of EF in influencing the behavioural symptoms of ASD. This very recent study conflicts with the fractionable triad approach as specific cognitive functions were not found to be uniquely associated with distinct ASD symptoms. Instead, Pellicano has suggested that there is unlikely to be one-to-one mapping between cognition and behaviour, and that different environmental interactions may affect the way in which cognition influences behaviour, and vice versa.

2.4 Towards a Multi-Faceted Cognitive Account of ASD: Questions and Future Directions

Single cognitive deficit models of ASD have attempted to reduce the varied behavioural symptoms of the condition to a single underlying cognitive deficit. These single deficit models

predict strong inter-correlation between performance on tests of ToM, EF and CC. The present review of the existing evidence suggests significant relations between ToM and EF, with some evidence of independence of CC from these abilities. The evidence on relations between cognitive test performance and real-life behaviour or symptoms is patchier, and it is interesting to speculate why test-symptom correlations are often non-significant. Clearly, one of the factors that interposes between individuals' underlying cognitive deficits or style and their behaviour or symptoms is their background of compensatory skills. The pattern of symptoms will reflect both the degree of impairment or cognitive style atypicality, and the alternative resources and abilities that the individual can bring to bear in order to compensate for, circumvent or alleviate those difficulties. While these will include measurable factors such as IQ and language abilities, they may also reflect differences in environment, intervention, memory, or attention. Johnson (2012) has proposed differences in EF as particularly important in compensatory skills. This might provide one explanation for the association found between ToM and EF in the work reviewed above. Work is needed to disentangle the effects of compensation, perhaps by contrasting implicit (e.g., 'anticipatory gaze', see Senju, et al., 2009) and explicit ToM task performance in relation to EF abilities in ASD.

Among other areas requiring further research is examination of developmental effects (e.g., Pellicano, 2013). What might we hypothesise about the relative fractionation of the triad across development? On the one hand, even primarily distinct abilities or traits might be hypothesised to become more inter-correlated with age, due to downstream effects. For example, even if reduced global integrative processing and ToM have independent origins, a child's tendency to interpret stimuli in a context-independent fashion might have developmental effects on their social skills; interaction might be sensitive to mental states but not to different contexts. Similarly, a child with poor inhibitory skills might be poorly tolerated by peers, have reduced social learning opportunities and develop less accurate social insight. On this view, studies with younger age groups will show clearer fractionation of symptom domains than studies with older groups.

However, the opposite hypothesis might also be proposed. Neuro-constructivist theories, and accounts of brain development postulating 'interactive specialisation', might suggest greater definition ('modularisation'; D'Souza & Karmiloff-Smith, 2011) of many cognitive abilities with age. Patterns of brain activation during some cognitive tasks become more specialised and

focal with age, and one might therefore predict greater differentiation of skills and cognitive functions with increasing age. Further longitudinal studies are needed to test which of these two predictions is correct.

Previous studies have used correlational analyses to assess the degree to which cognitive deficits and behavioural symptoms are associated (Joseph & Tager-Flusberg, 2004; Pellicano, 2010a; Pellicano, et al., 2006). However, these types of analyses cannot provide evidence of a direction of causality. Confirmatory factor analysis may be useful in assessing the underlying structure of the behavioural symptoms. Path analysis could be implemented to assess the degree of relation between cognitive processes and behaviour. More complex statistical methods could also be implemented to provide a more parsimonious approach, such as latent class analysis and factor-mixture modelling. These statistical techniques have the potential to provide additional information about cognitive and behavioural subtypes of ASD. For example, Georgiades et al. (2013) used factor-mixture modelling to suggest that the two ASD symptom domains of social-communicative impairments and RRBIs may be independent. The differing symptom profiles of severity suggested support for the existence of three homogeneous subgroups of ASD. Hypothetically, differing cognitive deficits may underlie the symptom profiles of these three subgroups of ASD. Additional analyses, such as latent growth modelling, could also be used to explore cognitive functioning across development and its altering relations with ASD symptoms using a longitudinal framework. These analyses could help test the multiple cognitive deficit model or fractionated triad theory of ASD.

The present chapter has been concerned with studies of ASD, but clearly of relevance to the fractionated triad account is the existence of other clinical groups in whom deficits in just ToM, just EF or just CC can be documented (see Happé & Ronald, 2008, for discussion). The new DSM-5 includes a new category of Social (Pragmatic) Communication Disorder, aimed in part at capturing those individuals who may have social and communication problems without RRBIs. It will be interesting and important to see how this influences research and to discover whether ToM, EF and/or CC are affected in such individuals.

If, as the fractionated triad account suggests, ASD is caused by different genes, neural patterns and cognitive components that influence distinct behavioural symptoms, then it is possible that intervention can target particular aspects of ASD while leaving other aspects valued by ASD-

self-advocates untouched. Understanding the fractionable or monolithic cognitive underpinnings of the autism phenotype has the potential to be both theoretically and practically informative.

2.5 The Present Thesis

From the review presented in this chapter, it can be concluded that very few studies have considered multiple cognitive deficits in relation to the behavioural symptoms of ASD. In addition, many previous studies have used correlational analyses to assess the degree to which cognitive domains are inter-related and their associations with the behavioural symptoms of ASD. It was suggested that further statistical methods could also be implemented to provide a more parsimonious approach, and this thesis endeavours to explore the predictions proposed using more complex statistical methods.

The data that is examined in this thesis originated from the Twins Early Development Study (TEDS) where one or both children met diagnostic criteria for ASD. A subsample of adolescents took part in the Social Relationship (SR) study, which is described, along with measures, in Chapter 3. Chapter 4 attempts to address the prevalence of multiple cognitive atypicalities in children with ASD, their unaffected co-twins and a control group. Chapters 5 and 6 investigate the predictions of the 'fractionated triad' theory that were presented in the current chapter; that 1) cognitive atypicalities are relatively independent from one another and that 2) different cognitive atypicalities underlie the distinct symptom domains of ASD. Chapter 7 examines the heritability of these cognitive atypicalities and the genetic and environmental overlap between cognitive atypicalities and ASD using genetic model-fitting analyses. Chapter 8 acknowledges the heterogeneity present within ASD and examines if different subgroups can be found within ASD, based on behavioural symptoms, and whether these subgroups differ in terms of age, gender, IQ, diagnosis, cognitive profiles, and comorbid symptoms.

Chapter 3 Methodology

All of the analyses presented in the empirical chapters of this thesis (Chapters 4 to 8) utilise data collected as part of the Social Relationship (SR) study. This chapter therefore provides more in-depth information about the SR study, including participant selection recruitment and diagnostic assessments, the battery of cognitive tasks, a subset of the questionnaires and the general procedure.

3.1 Participants

Participants were part of the Twins Early Development Study (TEDS), a population-based longitudinal study of all twins born in the UK between 1994 and 1996. The 12,054 families involved at the start of TEDS were reported to be representative of UK families (Haworth, Davis, & Plomin, 2013). An initial contact questionnaire gathered general background information about the twins and their family. Subsequently, families have returned information at 2, 3 and 4 years, at 7, 8 and 9 years, and at 10, 12, 14 and 16 years, with 18-year data collection under way. Various subsets of the initial sample have since been assessed by post, telephone, in-person or using web-based assessments to gather information about the twins' language, cognitive, and social development.

The Social Relationships Study (SR study) focused on those TEDS families with one or both twins meeting diagnostic criteria for ASD (see Figure 3.1 for a flow diagram to illustrate the sample selection procedure). Twins 'at risk' of ASD were identified a) from a parental report of an ASD diagnosis directly to TEDS (via phone at any point or by ticking boxes about diagnoses on postal questionnaires) and/or b) elevated scores on the Childhood Autism Spectrum Test (CAST) (Scott, Baron-Cohen, Bolton, & Brayne, 2002) at age 8 (data available from 8,941 TEDS families). 210 families reported a previous ASD diagnosis in at least one twin, and an additional 202 families had at least one child who scored above cut-off for suspected ASD on the CAST (≥15). Of these 412 families, 330 families were contactable and consented to take part in the second stage of screening. Families completed the ASD module of the Development and Wellbeing Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) via a telephone interview. This identified 203 families with at least one child who met DAWBA criteria for an ASD and so were invited to take part in the SR study. To address possible

selection bias and selective attrition in TEDS, a mail-out to child psychiatrists across the UK and advertisements through the National Autistic Society and the Twins and Multiple Births Association, were carried out to find any additional twin pairs with ASD born between 1994 and 1996. This yielded an additional five twin pairs. Informed parental consent was obtained from 129 families to complete a home visit, including diagnostic and cognitive testing; other families were not traceable or did not consent to in-person assessments. The 129 families who took part were comparable to those eligible for participation (i.e., CAST≥ 15 or suspected ASD) but who did not take part for CAST score (p = .14), socioeconomic status (p = .25) and zygosity (p = .23), with the exception of gender as more girls were in the 'high CAST/suspected ASD group' (36%) than the final sample (17%) (Colvert, et al., 2015). Twins in the ASD families who did not meet criteria for ASD comprised the unaffected co-twin group in the following thesis.

Participants were diagnosed with ASD using gold-standard diagnostic instruments; the ADI-R (Lord, et al., 1994) and the ADOS (Lord, et al., 2000). Additional cut-offs devised by the Autism Genetic Resource Exchange (AGRE) were implemented to identify family members with more subtle ASD symptoms and assigned cases to 'ASD' (AGRE categories Autism and 'Not Quite Autism'), 'Broad Spectrum Disorder', and 'unaffected'. A 'broad spectrum' diagnosis was permitted for the ADOS and corresponded to just below cut-off for diagnostic criteria for an ASD on the ADOS (-2 points). Participants were classified using available information (ADI-R, ADOS, DAWBA). In 37% of the ASD sample (N = 89), the ADI-R and the ADOS classifications were inconsistent. For these cases, diagnostic consensus was reached by a team of clinicians. One twin pair was excluded from analyses since neither twin reached diagnostic cut-off for ASD, but CAST score >12 rendered them unsuitable for inclusion in the control sample. Children were also excluded if there was knowledge of circumstances that may have affected the accuracy of diagnosis (N = 2). For analyses in the following chapters, ASD diagnoses and broad spectrum diagnoses were combined to create one ASD group to cover the complete autism spectrum from severely impaired individuals through to those with more subtle impairments. In the ASD group, 141 adolescents were diagnosed with ASD and 40 adolescents met the definition for a broad spectrum diagnosis. An unaffected co-twin group was also created consisting of 73 co-twins without an ASD or broad spectrum diagnosis.

A comparison control sample with CAST scores less than 12 was recruited via TEDS and matched to the ASD sample on gender, age, IQ, social economic status and zygosity. 80 control

twin pairs were recruited, making a total of 209 families visited in their homes by a team of two trained researchers.

The ASD group contained 181 adolescents (13 years 6 months; 150 males), the unaffected co-twin group contained 73 adolescents (13 years 6 months; 27 males) and the control group contained 160 adolescents (12 years, 10 months; 110 males).

Table 3.1 provides further information regarding the age, IQ, gender, zygosity, ADI and ADOS of the ASD, co-twin, and control group.

There was a significant difference between groups (ASD, co-twins, control) in age ($F(2,411) = 32.20$, $p < .001$, $\eta^2 = .135$). Tukey post-hoc tests revealed that the control group was significantly younger than both the ASD and co-twin groups ($p < .001$). There were significant differences in IQ across groups ($F(2,411) = 28.23$, $p < .001$, $\eta^2 = .121$). Overall, the ASD group ($M = 90.02$) had a significantly lower IQ score than both the co-twin group ($M = 104.76$, $p < .001$) and the control group ($M = 101.91$, $p < .001$). There were no significant differences on scores for IQ between the co-twin group and control group ($p = .476$).

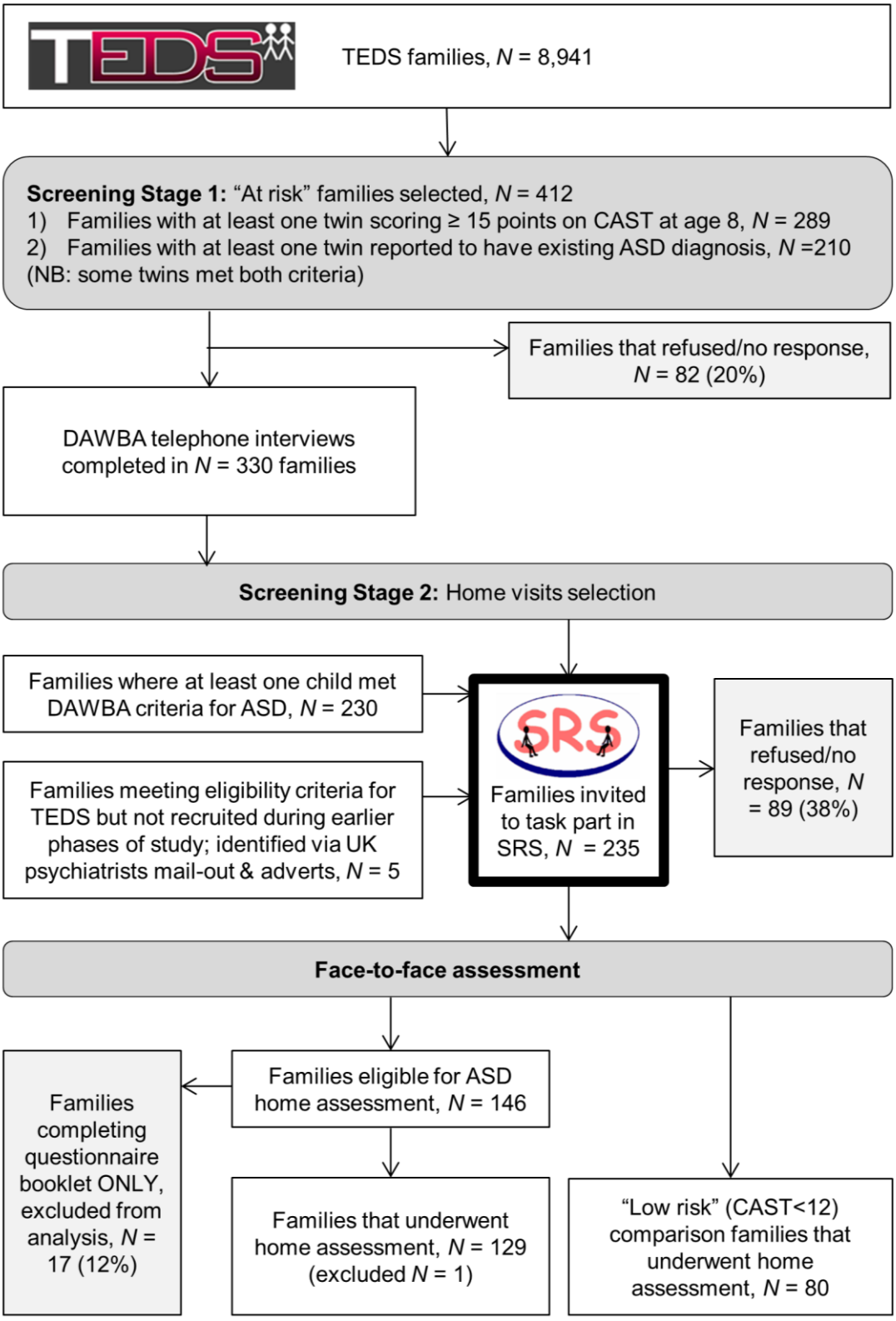


Figure 3.1. Social Relationships study (SR study) sample selection stages and the overall number of participants included

Table 3.1. Participant characteristics

	ASD				Unaffected Co-twins (CT)				Controls (TD)				Sig.
	N	*M*	*(SD)*	Range	*N*	*M*	*(SD)*	Range	*N*	*M*	*(SD)*	Range	*p*
Age (years)	181	13.49	(0.69)	12.08-16.25	73	13.50	(0.65)	12.25-15.17	160	12.79	(1.10)	10.92-15.58	< .001
IQ (WASI 2-subtest)	153	94.07	(16.91)	55-128	71	104.76	(13.73)	61-130	158	102.00	(15.19)	56-142	< .001
IQ (imputed score)	181	90.02	(20.34)	49-128	73	104.76	(13.54)	61-130	160	101.91	(15.14)	56-142	< .001
ADOS total (raw)†	174	11.38	(6.14)	0-26	71	1.83	(2.23)	0-10	-	-	-	-	< .001
ADI total†	177	37.64	(16.19)	3-70	72	5.46	(5.03)	0-23	-	-	-	-	< .001
Males:Females			4.84:1				1.70:1				2.20:1		< .001
MZ:DZ				27:100							28:52		.002

Abbreviations: ASD = autism spectrum disorder; CT = unaffected co-twins; DZ = dizygotic twin pairs; M = mean average; MZ = monozygotic pairs; N = number of participants; SD = standard deviation; TD = typically-developing controls

Note: †higher score = more severe

3.2 Measures

3.2.1 Diagnostic Measures

3.2.1.1 The Childhood Autism Spectrum Test (CAST)

The CAST is an informant-completed questionnaire based on behavioural descriptions of ASD as delineated in ICD-10 and DSM-IV. The 31 items are scored yes/no and summed; a cut-off score of 15 or above is reported to have 100% sensitivity, 97% specificity and a positive predictive value of 50% for a diagnosis of ASD (Williams et al., 2005). Parents completed the CAST when their twins were 8 years-old. A cut-off score of 15 was used to identify children at risk for ASD. In the first stage, children identified at risk of ASD were contacted to enrol in the SR study for further assessments.

3.2.1.2 The Developmental and Well-being Assessment (DAWBA)

Telephone interviews using the ASD-module of the DAWBA were used at the second stage of SR study enrolment and included 15 questions about social difficulties, 14 about repetitive, restricted behaviours and interests and three about developmental language milestones (Dworzynski, et al., 2009). A child received a DAWBA diagnosis of autism when the operational criteria in DSM-IV and ICD-10 were met. Asperger's diagnosis was given when parent reports indicated that all autism criteria were met but the child's early language development was not delayed and the child's intellectual ability was in the normal range. ASD (other) diagnosis was assigned if parents reported a minimum of three probable or two definite symptoms from the social difficulties domain, two probable or one definite symptom from the communication domain, and two probable or one definite symptom from the RRBI domain. Children who were assigned a diagnosis of autism/ASD/Asperger syndrome on the DAWBA were further assessed during home visits using the ADI-R and ADOS (described below).

3.2.1.3 Autism Diagnostic Interview (ADI-R)

The ADI-R (Lord, et al., 1994) is a well-established standardised assessment tool for ASD conducted as a semi-structured caregiver interview enquiring about current function and developmental history (93 items). The ADI-R is carried out in-person and takes two to three hours to complete. There are 111 items to assess the developmental history and current

behaviour of the individual being evaluated and focuses on three main aspects; language/communication, reciprocal social interaction, and RRBIs. Most items are scored from 0 (no impairment) to 3 (severe impairment) and scoring algorithms were used to create three different totals in communication, social interaction and RRBIs. For a diagnosis of autism based on the ADI-R, individuals must meet cut-offs in all three ADI domains and must meet the age of onset criteria (< 36 months). Additional cut-offs devised by the Autism Genetic Resource Exchange (AGRE) were implemented to identify family members with more subtle ASD symptoms and assigned cases to 'ASD' (AGRE categories Autism and 'Not Quite Autism'), 'Broad Spectrum Disorder', and 'unaffected'.

3.2.1.4 Autism Diagnostic Observation Schedule (ADOS)

The ADOS (Lord, et al., 2000) is a well-validated, semi-structured observational assessment and is considered a gold-standardised diagnostic tool alongside the ADI-R in ASD diagnosis. A trained examiner observed the child's response to a social interaction with an unfamiliar adult, and also used a series of interview-style questions. The ADOS provides behavioural information about a participant's reciprocal social interaction, language and communication, and RRBIs. This behaviour was then coded to create a diagnostic algorithm score to identify autism and ASD using clinical cut-offs (Gotham, et al., 2007). ASD and autism were combined to create one ASD category. A 'broad spectrum' diagnosis was also permitted for the ADOS and corresponded to just below cut-off for diagnostic criteria for an ASD on the ADOS (-2 points). The ADOS includes four modules dependent on the participant's language ability and chronological age. In the SR study, 133 participants completed Module 3 (for verbally fluent children), 1 participant completed Module 2, and 14 participants completed Module 1. Each ADOS assessment lasted approximately 30 to 50 minutes.

3.2.1.5 Best-Estimate Consensus Diagnosis

Best-estimate diagnoses were assigned, blind to zygosity and co-twin diagnostic status, following review of all available information (ADI-R, ADOS, DAWBA, clinical reports). When all available sources of information were in agreement, cases were assigned to that category. In 89 cases the diagnostic classifications across instruments were inconsistent. In these cases all available data were assessed by clinical experts and consensus best-estimate diagnoses were assigned on the basis of this review.

3.2.2 Questionnaire Measures

After the home visits, parents and the twin pairs were asked to complete a questionnaire booklet. Only the measures relevant to this thesis are described here.

3.2.2.1 Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) is a brief behavioural screening questionnaire completed by parents (*N* = 186) for children and adolescents aged 4- to 16-years-old. It consists of 25 statements, such as "Restless, overactive, cannot stay still for long" and allows the parent to indicate 2 ("certainly true"), 1 ("somewhat true") or 0 ("not true") (some items reverse coded as per scoring criteria). The SDQ contains 5 subscales with 5 items for each subscale; emotional symptoms, conduct problems, hyperactivity, peer problems, and pro-social behaviours. The total difficulties score (20 items) indicates normal (0-13), borderline (14-16), and abnormal behaviour (17-40). Subscale scores can also indicate normal, borderline, and abnormal behaviours in that specific domain (see http://www.sdqinfo.org/). A self-report version of the SDQ was also completed (*N* = 165) and asked about the same 25 items, but the wording was slightly different (Goodman, Meltzer, & Bailey, 1998). This self-report version is deemed suitable for 11- to 16-year-olds (Goodman, Meltzer, & Bailey, 1998).

3.2.2.2 Revised Children's Anxiety and Depression Scale

The Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000) is a 47-item questionnaire evaluating children's anxiety symptoms with subscales including; separation anxiety disorder, social phobia, generalised anxiety disorder, panic disorder, obsessive compulsive disorder, and major depressive disorder. The subscales yield a Total Anxiety Score (sum of the 5 anxiety subscales) with subclinical (t-score 60-69) and clinical cut-offs (t-score≥70). The current study did not include the subscale for major depressive disorder (10 items) due to its similarity with the SMFQ. The informant rated the items 0 ("never"), 1 ("sometimes"), 2 ("often"), or 3 ("always"), based on the last three months (RCADS-Child *N* = 164). A parent version of the RCADS was also used (*N* = 178), which assessed the parent's report of their twins' symptoms of anxiety across the same 5 subscales.

3.2.2.3 Short Mood and Feelings Questionnaire

The Short Mood and Feelings Questionnaire (SMFQ; Sharp, Goodyer, & Croudace, 2006) evaluates children's depressive symptoms and focuses on affective and cognitive symptoms. It asks how the child has been feeling or acting in the past two weeks and contains 13 items. The informant (SMFQ-Parent; *N* = 182; SMFQ-Child; *N* = 158) rated each item as 0 ("not true"), 1 ("somewhat true"), or 2 ("certainly true") to gain an overall total score (maximum = 26). Two of the items in the SMFQ were the similar to two items from the SDQ, and so each item was only asked once within the SDQ. Clinical cut-offs for the SMFQ-Parent (score ≥ 9) and SMFQ-Child (score ≥ 8) were based on Thapar and McGuffin (1998) suggestions. The total score from the SMFQ-Parent was used to index depression.

3.2.2.4 Toronto Alexithymia Scale

The Toronto Alexithymia Scale (TAS-20; Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994) was developed as a self-report measure of the alexithymia construct. It consists of 20 items representing 3 factors; difficulty identifying feelings (7 items), difficulty describing feelings (5 items) and externally-oriented thinking (8 items). In the current study, only 19 items were administered, which excluded one item from 'Difficulty Describing Feelings' ("It is difficult for me to find the rights words for my feelings"). The items were rated by the respondent on a 5-point Likert scale. The respondent was either the child (*N* = 71) or the parent (*N* = 86). Responses were totalled (range = 0-95) to provide a continuous variable.

3.2.2.5 Short Sensory Profile

The Short Sensory Profile (SSP; McIntosh, Miller, Shyu, & Dunn, 1999) is a 38-item questionnaire that identifies sensory problems in the tactile, taste/smell, movement and visual/auditory domains as well as under-responsiveness and sensory seeking behaviours in children via parental report. Items are rated on a 5-point scale ranging from 'never' (scored 5) to 'rarely' (4), 'occasionally' (3), 'frequently' (2), and 'always' (1). All SSP scores were reverse coded so that higher scores reflected greater levels of sensory abnormalities.

3.2.3 Cognitive Task Battery

The cognitive tasks were chosen as they were deemed appropriate for the age range and ability level of the participants. They provide a comprehensive assessment of a full range of cognitive abilities in individuals and are sensitive to cognitive deficits which have previously been described in individuals with ASD.

3.2.3.1 IQ

Intellectual ability was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) to obtain an estimated score for IQ. Fourteen nonverbal adolescents completed the Raven's Coloured Progressive Matrices (Raven, Raven, & Court, 1998) and the British Picture Vocabulary Scales-Revised (BPVS) (Dunn, Dunn, Whetton, & Pintillie, 1997) to obtain an estimated score for verbal and performance IQ. To include the low IQ individuals in the subsequent analyses, the 14 nonverbal children were given a provisional WASI full-scale IQ score of 49 (1 point below the lowest possible score on the WASI). The current study used the Block Design subtest as a measure of CC. Therefore, the two-subtest version of the WASI (includes Matrix Reasoning and Vocabulary) was used as an estimate of IQ.

3.2.3.2 Central Coherence Tasks

Six tasks designed to measure central coherence were administered.

3.2.3.2.1 Embedded Figures Test

A modified version of the Embedded Figures Test was used (EFT; Witkin, Oltman, Raskin, & Karp, 1971), including seven items from the children's version of the task (Children's Embedded Figures Test, CEFT; all 'house' shape items: 3, 4, 6, 9, 11, 12, 14) and eight items from Form A of the standard EFT (items 1, 4, 5, 6, 8, 10, 11, 12; Witkin et al., 1971) with one practice item before each set. Items were administered in numerical order, with the CEFT preceding the EFT. Participants were first shown a simple shape on a laminated sheet that remained in view. They were told that they would see a picture with the simple shape hidden in it and that the hidden shape would be the same size and shape as the simple shape. Timing began as soon as the complex shape was revealed and ended when the participant had found the simple shape (either by pointing or stating their success). To check that they were correct, participants were

then required to show the figure's location using a transparent acetate sheet with the simple figure printed on it. If they were incorrect, the participant was encouraged to look again and timing was resumed. A maximum of 60 seconds was allowed per search and a failure was recorded if the correct response was not given within this time.

Accuracy and reaction times (to the nearest second as measured on a stopwatch) were recorded. Accuracy was calculated by summing the total of correct items in both the CEFT and standard EFT with a maximum score of 15. Reaction times were calculated for correct trials only (White & Saldana, 2011).

3.2.3.2.2 Block Design Task

The Block Design Task was a subtest from the WASI that is used to measure perceptual organisation and general intelligence. The stimuli consisted of nine two-colour cubes and a set of 13 printed two-dimensional geometric patterns. Each cube (block) had two white sides, two red sides, and two half-red, half-white sides. The printed design patterns progressed in difficulty from simple designs requiring two cubes, to more complex designs requiring nine cubes.

The participant first completed two practice trials, in which the experimenter constructed two four-block designs, and the participant was then required to replicate the design. If they were incorrect, then the experimenter repeated the demonstration and the participant had a second attempt. If the participant failed at the second attempt, then a two-block design was administered.

The participant then completed 10 block designs in a fixed order according to the WASI Block Design procedure. The experimenter began timing after saying the last words of instructions and stopped when the participant indicated that they had finished the item. If the participant indicated that they had finished, and then realised that they had made an error, they were able to correct the design within the specified time limit. Once the participant had completed a design, then the blocks were scrambled and the next design was presented.

The experimenter recorded the accuracy of each construction (according to the scoring criteria in the WASI manual) and the time to complete the design in seconds. There was a time limit of 60 seconds for four-block designs and 120 seconds for nine-block designs. An error was recorded if the participant failed to construct the block design within the time limit.

3.2.3.2.3 Fragmented Pictures

The stimuli used were line drawings of an apple, a book, an elephant, a kite and a snowman (taken from Snodgrass & Vanderwart, 1980). Each object had eight levels of degradation, from total degradation (frame 1) to full view (frame 8). Participants were instructed to identify each picture at the most degraded level possible. The mean average frame at which each participant correctly identified the pictures was then calculated.

However, this task was not used in analyses in this thesis due to large amounts of missing data (*N* = 196).

3.2.3.2.4 Homographs Reading Test

The Homographs Reading Test was based on Happé (1997) procedure. The stimuli consisted of 16 test sentences and a set of 13 pre-test single words that included the homographs. Each test sentence appeared on a separate A4 page, printed across a single line (landscape orientation). Four of the original five homographs from Happé (1997) were used (*tear, row, lead,* and *bow*).

Participants were first asked to read aloud 13 pre-test single words which included the homographs (e.g., *tear, read, lead,* and *bow*) to assess reading ability and familiarity with the homographs. Following this, the participant was presented with 16 test sentences. The test sentences contained four different conditions; frequent pronunciation before context (e.g., “There was a big *tear* in her eye”), frequent pronunciation after context (e.g., “Molly was very happy, but in Lilian’s eye there was a big *tear*”), rare pronunciation before context (e.g., “There was a big *tear* in her dress”), and rare pronunciation after context (e.g., “The girls were climbing over the hedge. Mary’s dress remained spotless, but in Lucy’s dress was a big *tear*”). The test sentences were presented one at a time in a fixed, pseudo-random order with no two homographs presented consecutively. The participant was required to read aloud the written test sentence and the pronunciation of the homograph and any self-corrections made by the participant were recorded. The participant also completed a post-test in the form of a picture-vocabulary test to assess the participant’s knowledge of each homograph.

Participants had to demonstrate that they knew all meanings and pronunciations for at least two of the four homographs on the post-test for their results to be considered valid. The overall total

number of homographs pronounced appropriately in each condition was calculated (maximum = 4). The total number of homographs pronounced appropriately before context was calculated (before context total; maximum = 8) by adding the two conditions; frequent pronunciation before context and rare pronunciation before context. The total number of homographs pronounced appropriately after context was calculated (after context total; maximum = 8) by adding the two conditions; frequent pronunciation after context and rare pronunciation after context. An overall effect of context was then calculated (effect of context = after context total minus before context total).

3.2.3.2.5 Planning Drawing Task, Part A

The Planning Drawing Task was adapted from Booth, et al. (2003). Participants were required to copy a picture of a house and snowman, presented in that set order. The participant was shown a picture and told "*this is a picture of a [house/snowman] that I drew earlier. I want you to draw a picture of a [house/snowman] like mine*". The picture was then left in view of the participant. The drawing process was videotaped for later analysis and the experimenter noted the first feature drawn and the order that the features were drawn.

The participants were scored on three aspects of the drawings for a detail-focused style; the *initial features* drawn (local feature = 2, 'in-between' = 1, global feature/outline = 0), the *fragmentation* of the drawing (fragmented = 2, some fragmentation = 1, no fragmentation = 0), and the *configuration* of the drawing (poor final configuration = 2, some configuration = 1, good configuration = 0). These scores were then summed to create an overall weak coherence score (maximum = 12).

3.2.3.2.6 Sentence Completion Task

The Sentence Completion Task, as described in Booth and Happé (2010), consisted of ten sentence stems plus five control sentences. The task began with a practice sentence: "*He cleaned up the mess with a brush and…*". Ten test sentence stems were then presented to the participants, which were designed to produce a conflict between making an appropriate global completion or a locally cued response. Participants were instructed to complete a sentence that the experimenter started, e.g., *"The sea tastes of salt and …"*, with a local response being *"pepper*", and a correct global response being "*seaweed*". Five control sentence stems were

also included that did not produce a local-global conflict for their completion (e.g., *"A vet cares for cats and…"*). These control sentences were interspersed with test sentences in a set order for all participants. Sentence completions could be a single word or a phrase. Responses were written down by the experimenter and audio taped for later scoring.

An error score was calculated based on scoring criteria developed by Booth (2006). Scoring was based on participants' initial response. A 3-point scoring system was used; 0 for a globally meaningful completion within 10 seconds; 1 for no response, a response delay greater than 10 seconds, or an 'odd' response that was not a local completion; 2 for a local completion that was not meaningful in the context of the whole sentence. The error score was then summed to give a total error score out of 20 for the ten test sentences.

3.2.3.3 Executive Function Tasks

Four tasks designed to measure different aspects of executive function were administered, providing measures of planning (Planning Drawing task), mental flexibility (ID/ED), mental initiation (Letter Fluency Task), and inhibitory control (Luria Hand Game).

3.2.3.3.1 Letter Fluency (FAS) Task

The Letter Fluency Task followed Turner's (1999) procedure. Participants were required to generate as many different words as possible beginning with the letters F, A, and S. For each letter, the participant was given 30 seconds and was instructed not to use proper nouns or repeat the same word with different endings. The mean number of correct responses was calculated.

3.2.3.3.2 Luria Hand Game

The Luria Hand Game was used to assess inhibitory control (see Hughes, 1996, for procedure). The participant was told that they were going to play a hand-game and were asked to copy the experimenter's hand gestures. Firstly, the experimenter and participant placed their hands behind their backs. The experimenter than produced either a fist or pointed a finger and the participant was required to copy the experimenter's hand gesture. When the participant had successfully imitated three points and three fists, then the experimenter introduced the test condition. The experimenter told the participant that if the experimenter made a fist, then the

participant was to point their finger, and if the experimenter pointed their finger, then the participant was to make a fist. The test condition was discontinued when the participant successfully completed five consecutive trials, with a maximum of ten trials. A total score was calculated by totalling the number of initial correct responses from the test condition and dividing it by the number of trials that the participant completed, then multiplying this number by ten.

3.2.3.3.3 Intra-/Extra-Dimensional (ID/ED) Shift Task

The ID/ED task (from the Cambridge Neuropsychological Test Automated Battery) was presented on a computer and followed Hughes, et al. (1994) procedure. There were a maximum of nine stages (Table 3.2). On each trial, two test stimuli were presented in one of four boxes (top, bottom, right or left of the screen). The participant was told "*One of these patterns is correct, and one of the patterns is wrong. Have a guess at which pattern is correct".* They were then told to keep choosing one of the two stimuli and the correct choice followed a rule that changed occasionally. Participants were given feedback in the accuracy of their responses, with the box turning green if the correct choice was made, and a red box if the choice was incorrect. The criterion for progressing on to the next stage was a run of eight correct choices within 50 trials. The rule reversed on trial 2, 5, 7 and 9 and the number of errors was recorded. This was used to create the mean number of reversal errors.

Table 3.2. The nine stages in the ID/ED task.

Stage	Type	Test stimuli	Relevant dimension	Correct stimuli
1	Simple discrimination	Shape A Shape B	Shape	Shape A
2	Simple reversal	Shape A Shape B	Shape	Shape B
3	Compound discrimination	Shape A adjacent to Line A Shape B adjacent to Line B	Shape	Shape B
4	Compound discrimination	Line A superimposed on Shape A Line B superimposed on Shape B	Shape	Shape B
5	Compound reversal	Line A superimposed on Shape A Line B superimposed on Shape B	Shape	Shape A
6	Intradimensional shift	Line C superimposed on Shape C Line D superimposed on Shape D	Shape	Shape C
7	Intradimensional reversal	Line C superimposed on Shape C Line D superimposed on Shape D	Shape	Shape D
8	Extradimensional shift	Line E superimposed on Shape E Line F superimposed on Shape F	Line	Line E
9	Extradimensional reversal	Line E superimposed on Shape E Line F superimposed on Shape F	Line	Line F

3.3.1.1.1 Planning Drawing Task, Part B

Part B of the Planning Drawing Task immediately followed Part A. When the drawing from Part A was complete, the original and the copy of the picture were removed. Another blank sheet of paper was provided and the participant was told "*now I want you to draw another picture of a [house/snowman], but this time draw it with [four windows/teeth]"*. The drawings were then rated and given an *allowance score* based on the degree of advanced planning that was evident to accommodate the additional features. Two points were given when a clear and effective allowance was made (e.g., extra spacing), one point for some allowance but not enough to

prevent the drawing from appearing cramped, and zero points for no allowance. A total allowance score (0 - 4) was then calculated for each participant.

3.3.1.2 Theory of Mind Tasks

3.3.1.2.1 Penny Hiding Game

The Penny Hiding Game procedure followed the original procedure introduced by Baron-Cohen (1992). This task tests the ability of the participant to deceive the experimenter and depend on self-awareness and mentalising ability. This game is a two-person game, in which the participant is a guesser in the first condition and a hider in the second condition. The hider hides a penny in either their right or left hand, and the guesser guesses which hand the penny is hidden in. In the first condition, the experimenter was the hider and the participant was the guesser. The roles changed in the second condition; the participant was the hider and the experiment was the guesser. The number of errors or tricks the participant used in the second condition was noted (see Baron-Cohen, 1992, for description of errors and tricks). The errors recorded were; both hands were not kept out of sight whilst holding the penny, only one hand was used, hand(s) were open, told where the penny is, or a display error (the penny was hidden but can tell where it is, i.e., by grip). The game was discontinued after four trials if the participant displayed no tricks or errors, with a maximum of six trials. The total number of errors across trials was calculated.

3.3.1.2.2 Triangles Animation Task

The stimuli were developed by Abell, et al. (2000). Participants watched short silent cartoons (34 to 45 seconds) depicting one large red and one small blue triangle moving about on screen within an enclosure. The current study only used the theory of mind (ToM) movement sequences; surprising, coaxing, mocking, and seducing. These sequences showed one triangle reacting to the other triangle's mental state. For example, in the coaxing sequence, the big triangle is seen to coax the little triangle out of the enclosure. The triangles within the ToM sequences can be identified as people, for example, mother and child. Participants were then required to tell the experimenter what had happened in each cartoon.

Accuracy of response was coded as 0, 1 or 2 (maximum = 8). A response was scored as 2 if the response met the intended meaning of the animation, with 1 scored for a partially accurate

response. Intentionality of response was coded 0 through to 5 (maximum = 20). A score of 4 or 5 was given for responses that included mention of psychological states and so were classified as mentalising. Responses that mentioned interaction between the triangles, with no mention of mental state, were classified as interaction and given a score of 3. Responses that only described a simple action with no mention of interaction of mental states, was classified as an action and was given a score of 0. A total mentalising score (maximum = 4) was calculated by scoring 1 if participants scored 4 or 5 on the intentionality score (maximum = 5), only if an accurate description (a score of 1 or 2) was given. A mentalising score of 0 was given if participants scored 0 to 3 on intentionality score or if their responses were inaccurate. This method of scoring was used as children with ASD have been previously shown to provide mentalising descriptions to ToM animations as frequently as typically-developing 8-year-olds, but these mentalising descriptions were found to be inappropriate as compared to typically-developing 8-year-olds (Abell, et al., 2000). This method of scoring therefore takes this finding into account.

3.3.1.2.3 False-Belief Stories

Participants were told four separate false-belief stories; “Pencil-Box”, “Sally-David”, “Chocolate” (Figure 3.2) and “Seaside” (Figure 3.3). All of the stories contained a first-order false-belief question, and the Chocolate and Seaside stories each contained a second-order false-belief question. However, as so few participants completed Sally-David (*N* = 41), it was not used in the analyses in the thesis. Participants scored 0 for a false-belief question if they were incorrect or if they were incorrect on the control questions. Participants were rarely correct on the false-belief question and incorrect on the control questions (*N* = 10 for first-order false-belief; *N* = 23 for second-order false-belief). Participants scored 2 for a false-belief question if they answered correctly and were also correct on the control questions. A first-order false-belief score (maximum = 6) and a second-order false-belief score (maximum = 4) were totalled (maximum = 10).

Part A. First-Order False-Belief

"This is Mary and her brother John. Their Grandad has given them some chocolate to share. 'Put it away now' says Grandad, 'You can have it when Mum says so'. John & Mary go inside and put the chocolate in the fridge. Then they go out to play in the garden. Later, John comes in for a glass of water. He goes in the fridge and sees the chocolate. He wants to keep the chocolate all for himself, so he takes the chocolate out of the fridge and puts it in his bag."

First-order question: Where does Mary think the chocolate is?

Control question: Where has John put the chocolate really?

Part B. Second-Order False-Belief

"But look, Mary is playing by the window and she sees John putting the chocolate in his bag! John is so busy hiding the chocolate that he doesn't see Mary watching him through the windows. Later, Mum comes to call John and Mary for tea. She says they can have some chocolate now. John and Mary come running into the kitchen"

Second-order question: Where does John think Mary will look for the chocolate?

Reality question: Where is the chocolate really?

Memory question: Where was the chocolate first of all?

Figure 3.2. Chocolate story from false-belief stories

Part A. First-Order False-Belief

"This is Susan and her friend Tom. They are planning a trip to the seaside in Brighton and can go by either train or bus. The day before their trip they go to the train station to check train times and the bus station to check the bus times. The bus journey takes much longer so they decide to catch the 9:00 train the next morning. Susan tells Tom that she will meet him at his house the next morning so they can walk to the train station together."

Memory question: How are Tom and Susan planning to travel to the seaside?

Reality question: Where have Tom and Susan agreed to meet?

"The next morning, Tom decides to go to the station early to buy the tickets, because he is worried that the queue at the ticket office will be very long. However, when he arrives he discovers that all the trains to Brighton have been cancelled."

Reality question: Does Tom know the trains have been cancelled?

First-order question: Does Susan know the trains have been cancelled?

Part B. Second-Order False-Belief

"Tom decides to go straight to the bus station to check if it is possible to buy bus tickets for the journey to the seaside. As she is getting ready to leave the house, Susan sees on the news that the trains have been cancelled."

Control question: Does Susan know the trains have been cancelled?

"She walks over to Tom's house and rings the bell. Tom's mum tells Susan that Tom left early to buy the tickets to the seaside."

Second-order question: Where does Susan think Tom has gone to buy the tickets?

Justification question: Why does she think that?

Reality question: Where has Tom really gone to buy the tickets?

Memory question: How did Tom and Susan originally plan to travel to the seaside?

Figure 3.3. Seaside story from false-belief stories

3.4 Procedure

Home visits took place from 2007 to 2009 and were made to all ASD and control families by two trained researchers. The ASD families completed two home visits, which lasted approximately six hours in total. The ASD families completed gold standard diagnostic assessments; the ADOS (Lord, et al., 2000) and the ADI-R (Lord, et al., 1994). The control families completed one home visit, which lasted approximately two hours. Both the ASD and control families completed an extensive cognitive battery to measure IQ, language ability, central coherence, executive function and theory of mind ability. The batteries were administered in a counterbalanced order with two fixed orders of tasks. The order of these tasks is shown in Figure 3.4. A different experimenter assessed each participant within the twin pair in order to reduce possible experimenter bias.

After the home visits, parents and the twin pairs were asked to complete a questionnaire booklet, including questions about their behaviours, anxiety, mood and feelings, emotions, and sensory behaviours. Parents were also asked to give information about their child's health and family history. The same parent completed the questionnaire booklet for both twins. A complete list of measures used in the SR study can be found in Appendix 1.

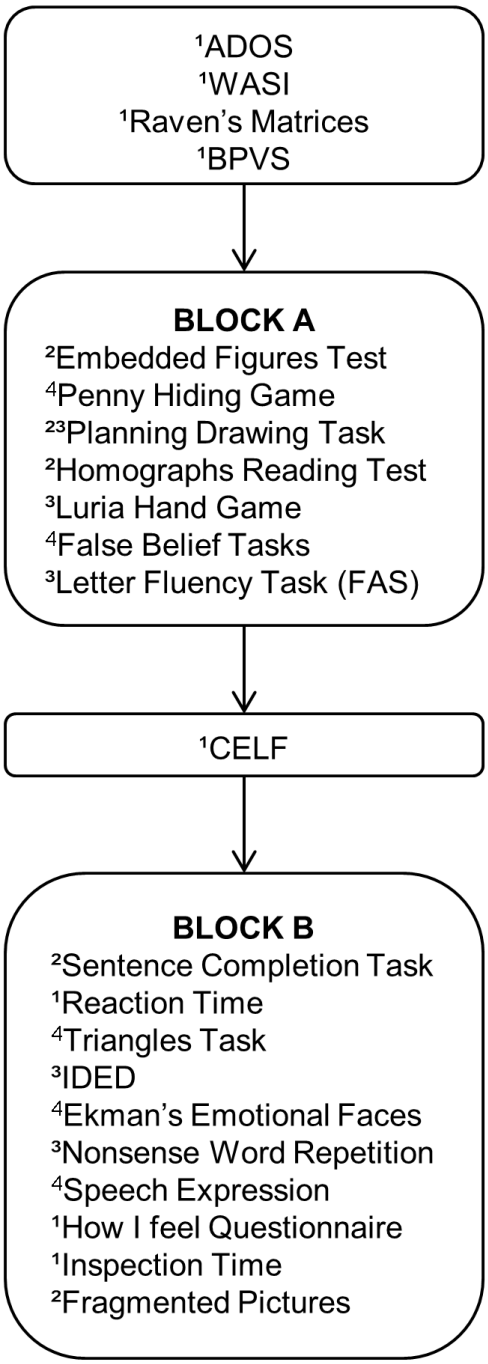


Figure 3.4. A flowchart to illustrate the order of the measures in SR study

Abbreviations: ADOS = Autism Diagnostic Observation Schedule; BPVS = British Picture Vocabulary Scales; CELF = Clinical Evaluation of Language Fundamentals; ID/ED = Intra-/Extra-Dimensional Shift Task; WASI = Wechsler Abbreviated Scale of Intelligence

Note. [1] = baseline task, [2] = central coherence task, [3] = executive function task, [4] = social cognition task.

Chapter 4 Exploring the Cognitive Features in Children with Autism Spectrum Disorder, Their Co-Twins, and Typically-Developing Children within a Population Sample

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4.1 Abstract

Background: The behavioural symptoms of autism spectrum disorder (ASD) are thought to reflect underlying cognitive deficits/differences. The findings in the literature are somewhat mixed regarding the cognitive features of ASD. The present study attempted to address this issue by investigating a range of cognitive deficits and the prevalence of multiple cognitive atypicalities in a large population-based sample comprising children with ASD, their unaffected co-twins, and typically-developing comparison children.

Methods: Participants included families from the Twins Early Development Study (TEDS) where one or both children met diagnostic criteria for ASD. Overall, 181 adolescents with a diagnosis of ASD and 73 unaffected co-twins were included, plus an additional 160 comparison control participants. An extensive cognitive battery was administered to measure IQ, central coherence, executive function, and theory of mind ability.

Results: Differences between groups (ASD, co-twin, control) are reported on tasks assessing theory of mind, executive function, and central coherence. The ASD group performed atypically in significantly more cognitive tasks than the unaffected co-twin and control groups. Nearly a third of the ASD group presented with multiple cognitive atypicalities.

Conclusions: Multiple cognitive atypicalities appear to be a characteristic, but not universal feature, of ASD. Further work is needed to investigate whether specific cognitive atypicalities, either alone or together, are related to specific behaviours characteristic of ASD.

4.3 Introduction

Autism spectrum disorder (ASD) is a developmental disorder characterised by impaired social interaction and communication, and restricted and repetitive patterns of behaviour and interests (RRBIs) (American Psychiatric Association, 2013). These behavioural symptoms are thought to reflect underlying cognitive deficits/differences, which have been extensively researched (see Brunsdon & Happé, 2014, for review). Findings to date have been somewhat mixed, perhaps due to methodological factors and the inherent heterogeneity within the autism spectrum. The current study attempts to address this issue by investigating a range of cognitive atypicalities in a large population-based sample comprising children with ASD, their co-twins, and typically-developing comparison children (termed 'controls').

Cognitive accounts of ASD can be broadly divided into domain-specific and domain-general theories. Domain-specific theories situate the primary deficit in social processing. Prominent amongst these is the 'Theory of Mind' (ToM) deficit account, which explains the social and communication impairments of ASD as resulting from difficulty representing mental states (e.g., Frith, et al., 1991b). This account has been influential in psychological research, neuroimaging and intervention, although the universality and specificity of ToM deficits has been questioned (Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998). Whether ToM deficits are primary or result from earlier abnormalities of social orienting or social motivation is also a topic of much debate (Dawson, et al., 2005; Jones, et al., 2008).

Domain-general accounts of ASD propose that the primary deficit/difference is not in social cognition specifically but lies in, for example, 'executive functions' (EF; Hill, 2004). Executive dysfunction in ASD has been proposed to underlie RRBIs due to a failure to generate new behaviours or shift set. Executive dysfunction has also been hypothesised to explain social/communicative deficits (Kenworthy, et al., 2009).

A number of domain-general accounts suggest areas of superior processing or differences in cognitive style, such as 'weak central coherence' (CC) (Frith, 1989; Happé & Booth, 2008; Pellicano, 2010a), a bias towards featural processing and reduced configural processing. Superior local processing, but accompanied by intact global processing, is also proposed by

'enhanced perceptual processing' (Mottron, et al., 2006), 'systemising' (Baron-Cohen, 2009) and enhanced discrimination (O'Riordan & Plaisted, 2001) accounts of ASD.

Traditionally, cognitive accounts of ASD have attempted to explain parsimoniously both socio-communicative impairments and RRBIs as resulting from a single underlying deficit/difference. However, more recently it has been suggested that multiple cognitive accounts may apply, with each explaining distinct symptoms of ASD (Brunsdon & Happé, 2014; Happé & Ronald, 2008; Happé, Ronald, et al., 2006). Thus, ASD might be seen as the result of a combination of cognitive deficits or atypicalities, with ToM deficits explaining socio-communicative features, executive dysfunction explaining RRBIs, and detail-focus (e.g., CC) explaining uneven cognitive profile and assets. Previous work has been limited in its scope to examine this hypothesis as most studies have investigated a single cognitive domain, with the notable exceptions of studies by Pellicano (Pellicano, 2013; Pellicano, et al., 2006) and Charman et al. (2011).

The aim of this study was to address the mixed findings in the literature regarding the cognitive features of ASD and to investigate the prevalence of multiple cognitive atypicalities in ASD. Previous studies, which have reported mixed findings, have typically had sample sizes of 15 to 40 individuals with ASD, and have often given tests of only one area of cognition. We aimed to test weak CC, EF and ToM in the same large sample of individuals with ASD. Mixed findings may also reflect differences in sample selection and recruitment (e.g., through specialist clinics, special schools, parent volunteers). We therefore tested a population-based sample, identified as meeting diagnostic criteria for ASD from a longitudinal study of all twins born in the UK in 1994-6. In addition, we assessed along with the ASD twins, their unaffected co-twins, who may be expected to share some (subclinical) traits or cognitive characteristics, according to family studies of the 'broader autism phenotype' (Hughes, Plumet, & Leboyer, 1999). Therefore, the current study included individuals across the range of ASD traits as well as typically-developing comparison participants.

4.4 Method

4.4.1 Participants

The ASD group contained 181 adolescents (13 years 6 months; 150 males), the unaffected co-twin group contained 73 adolescents (13 years 6 months; 27 males) and the control group

contained 160 adolescents (12 years, 10 months; 110 males). Table 4.1 provides further information regarding the age, IQ, gender, zygosity, ADI and ADOS scores of the ASD, co-twin, and control group.

There was a significant difference between groups (ASD, co-twins, control) in age ($F(2,411) = 32.20$, $p < .001$, $\eta^2 = .135$). Tukey post-hoc tests revealed that the control group was significantly younger than both the ASD and co-twin groups ($p < .001$). There were significant differences in IQ across groups ($F(2,411) = 28.23$, $p < .001$, $\eta^2 = .121$). Overall, the ASD group ($M = 90.02$) had a significantly lower IQ score than both the co-twin group ($M = 104.76$, $p < .001$) and the control group ($M = 101.91$, $p < .001$). There were no significant differences in IQ scores between the co-twin and control groups ($p = .476$).

Table 4.1. Participant characteristics

	ASD				Unaffected Co-twins (CT)				Controls (TD)				Sig.
	N	*M*	*(SD)*	Range	*N*	*M*	*(SD)*	Range	*N*	*M*	*(SD)*	Range	*p*
Age (years)	181	13.49	(0.69)	12.08-16.25	73	13.50	(0.65)	12.25-15.17	160	12.79	(1.10)	10.92-15.58	< .001
IQ (WASI 2-subtest)	153	94.07	(16.91)	55-128	71	104.76	(13.73)	61-130	158	102.00	(15.19)	56-142	< .001
IQ (imputed score)	181	90.02	(20.34)	49-128	73	104.76	(13.54)	61-130	160	101.91	(15.14)	56-142	< .001
ADOS total (raw)†	174	11.38	(6.14)	0-26	71	1.83	(2.23)	0-10	-	-	-	-	< .001
ADI total†	177	37.64	(16.19)	3-70	72	5.46	(5.03)	0-23	-	-	-	-	< .001
Males:Females			4.84:1				1.70:1				2.20:1		< .001
MZ:DZ					27:100						28:52		.002

Abbreviations: ASD = autism spectrum disorder; CT = unaffected co-twins; DZ = dizygotic twin pairs; M = mean average; MZ = monozygotic pairs; N = number of participants; SD = standard deviation; TD = typically-developing controls

Note: †higher score = more severe

4.4.2 Measures

4.4.2.1 Intellectual Ability

Intellectual ability was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) to obtain an estimated score for IQ. Fourteen nonverbal adolescents completed the Raven's Coloured Progressive Matrices (Raven, et al., 1998) and the British Picture Vocabulary Scales-Revised (BPVS) (Dunn, et al., 1997) to obtain an estimated score for verbal and performance IQ. To include the low IQ individuals in the subsequent analyses, the 14 nonverbal children were given a provisional WASI full-scale IQ score of 49 (1 point below the lowest possible score on the WASI). The current study used the Block Design subtest as a measure of CC. Therefore, the two-subtest version of the WASI (includes Matrix Reasoning and Vocabulary) was used as an estimate of IQ.

4.4.2.2 Cognitive Task Battery

The measures (with the targeted components), key variables, number of trials, and reference to procedure are shown in Table 4.2.

Table 4.2. Battery of cognitive tasks used in Social Relationship Study (SR study) by cognitive domain with references to studies describing task procedure

Cognitive Measure	Key Variable	Number of Trials	Reference for Task Procedure	Expected Direction of Group Effects
Central Coherence				
Embedded Figures Test (EFT)	Reaction time (seconds)	15 trials; 7 items from child EFT, 8 items from standard EFT	Shah & Frith (1983)	TD > ASD
Block Design Task	Accuracy	10 trials	Shah & Frith (1993)	ASD > TD
Homographs Reading Test	Context effect	16 sentences	Happé (1997)	TD > ASD
Planning Drawing Task, Part A	Coherence score	2 items; house & snowman	Booth, et al. (2003)	TD > ASD
Sentence Completion Task	Error score	10 sentences (plus 5 control)	Booth & Happé (2010)	TD > ASD
Executive Function				
Letter Fluency Task (FAS) *(mental initiation)*	Number of correct responses	3 trials; F, A, S	Turner (1999)	TD > ASD
Luria Hand Game *(inhibition)*	Conflict score	10 trials	Hughes (1996)	TD > ASD
Intradimensional/Extradimensional Task (ID/ED) *(cognitive set-shifting)*	Reversal errors	9 stages; progress on to next stage after 8 correct trials within 50 trials.	Hughes, et al. (1994)	TD > ASD
Planning Drawing Task, Part B *(planning)*	Planning score	2 items; house & snowman	Booth, et al. (2003)	TD > ASD
Theory of Mind				
Penny Hiding Game	Error score	6 trials	Baron-Cohen (1992)	TD > ASD
Triangles Animation Task	Mentalising score	4 trials; ToM only	Abell, et al. (2000)	TD > ASD
False-Belief Stories	First- and second-order false-belief score	3 stories; 3 first-order, 2 second-order questions	Perner, Frith, Leslie, & Leekam (1989)	TD > ASD

4.4.3 Procedure

Home visits were made to all ASD and control families by two trained researchers. The ASD families completed two home visits, which lasted approximately six hours in total. The ASD families completed gold standard diagnostic assessments; the ADOS (Lord, et al., 2000) and the ADI-R (Lord, et al., 1994). The control families completed one home visit, which lasted approximately two hours. Both the ASD and control families completed an extensive cognitive battery to measure IQ, language ability, CC, executive function (EF) and ToM ability. The batteries were administered in a counterbalanced order with two fixed orders of tasks. A different experimenter assessed each participant within the twin pair in order to reduce possible experimenter bias.

4.5 Results

All twins were treated as singletons in the present analyses to allow comparisons between groups of adolescents with ASD (termed ASD group), unaffected co-twins, and a control group. The reaction time from Embedded Figures Test (EFT), total error score in the Sentence Completion Task, the coherence score and planning score from the Planning Drawing Task, reversal errors in ID/ED, and errors in Penny Hiding Game were reflected so that a higher score indicated better performance in all tasks.

Preliminary data analyses indicated that some of the data did not meet assumptions of a normal distribution. Data from six of the cognitive measures were skewed (value > 2) and data from four of the cognitive measures had a leptokurtic distribution (value > 3). All variables were normalised using a Van der Waerden transformation.

Pearson's correlation analyses were carried out to investigate if age and IQ were related to performance on cognitive measures. For all groups, age was not significantly correlated with cognitive measures, except for Block Design Task performance in the ASD and control groups (ASD: r = -.24, p < .01, controls: r = -.44, p < .001). In the ASD group, IQ was significantly related to performance on most cognitive measures (12/13, all rs > .21, all ps < .01), except for Homographs Reading Test (r = .14, p = .094). Correlational analyses revealed fewer significant relationships between IQ and performance on cognitive measures for the unaffected co-twin group (2/13 measures) and the control group (4/13) as compared to the ASD group. Therefore,

IQ-adjusted standardised residuals for cognitive task performance were used in all further analyses (unless otherwise stated). The standardised residuals for the ASD and co-twin group are obtained from the regression line fit when fitting each cognitive measure as a dependent variable in a linear model with IQ as a predictor variable, according to the control group (Thomas, et al., 2009).

Table 4.3 shows the mean performance (raw scores) for each CC, EF, and ToM measure by group. One-way analyses of variance (ANOVA) to investigate group differences (ASD, co-twins, controls) in cognitive task performance are reported in Table 4.3, with post-hoc comparisons using Tukey tests. Figure 4.1 shows the mean performance of the ASD group and the unaffected co-twin group relative to the control group on all cognitive measures.

Table 4.3. Performance on cognitive measures for ASD and comparison groups (raw scores) and group differences for cognitive measures (transformed scores)

Measure	ASD			Unaffected Co-twins (CT)			Controls (TD)			Group differences (IQ-adjusted residuals; $p < .05$)			
										ANOVA			*Post-Hoc Tukey*
	N	*M*	*(SD)*	*N*	*M*	*(SD)*	*N*	*M*	*(SD)*	*F*	*p*	η^2	
Central Coherence													
EFT (reaction time, seconds)†	159	20.40	(10.70)	70	17.64	(7.71)	158	17.90	(9.32)	0.31	.733	.002	n.s
Block Design Task (score)	154	49.55	(13.02)	71	53.07	(10.60)	151	53.07	(10.58)	0.89	.410	.005	n.s
Homographs Reading Test (context effect)	138	1.70	(1.67)	71	2.13	(1.29)	151	2.12	(1.31)	3.91	.021	.021	TD > ASD (CT n.s.)
Sentence Completion Task (error score, max = 20)†	154	3.51	(3.02)	66	2.46	(2.64)	158	2.28	(2.49)	7.38	.001	.038	ASD > TD, CT
Planning Drawing A (coherence score, max = 12)†	158	1.15	(0.93)	71	0.82	(0.74)	156	0.80	(0.73)	9.89	< .001	.049	ASD > TD, CT
Executive Function													
Letter Fluency Task (score)	146	5.26	(2.63)	69	5.23	(2.17)	149	5.53	(2.51)	0.83	.438	.005	n.s
Luria Hand Game (conflict score, max = 10)	145	8.44	(2.72)	69	9.51	(1.13)	142	9.78	(0.60)	26.95	< .001	.132	TD, CT > ASD
ID/ED (error score)†	149	2.68	(2.69)	71	2.19	(2.32)	155	1.92	(1.62)	3.58	.029	.019	ASD > TD (CT n.s.)
Planning Drawing B (planning score, max = 4)	158	1.22	(1.01)	71	0.97	(0.89)	156	0.82	(0.82)	5.41	.005	.028	TD > ASD (CT n.s.)
Theory of Mind													
Penny Hiding Game (error score)†	148	0.98	(1.93)	68	0.54	(1.11)	152	0.11	(0.50)	19.04	< .001	.094	ASD > CT > TD
Triangles Animation Task (mentalising score, max = 4)	138	1.38	(1.26)	66	2.56	(1.21)	148	1.68	(1.21)	8.20	< .001	.045	CT > TD > ASD
False-Belief Stories (score, max=10)	134	9.22	(1.34)	69	9.88	(0.47)	153	9.77	(0.69)	12.50	< .001	.066	TD, CT > A SD

Abbreviations: ASD = autism spectrum disorder; CT = unaffected co-twins; EFT = Embedded Figures Test; M = mean average; N = number of participants; n.s = not significant; SD = standard deviation; TD = typically-developing controls

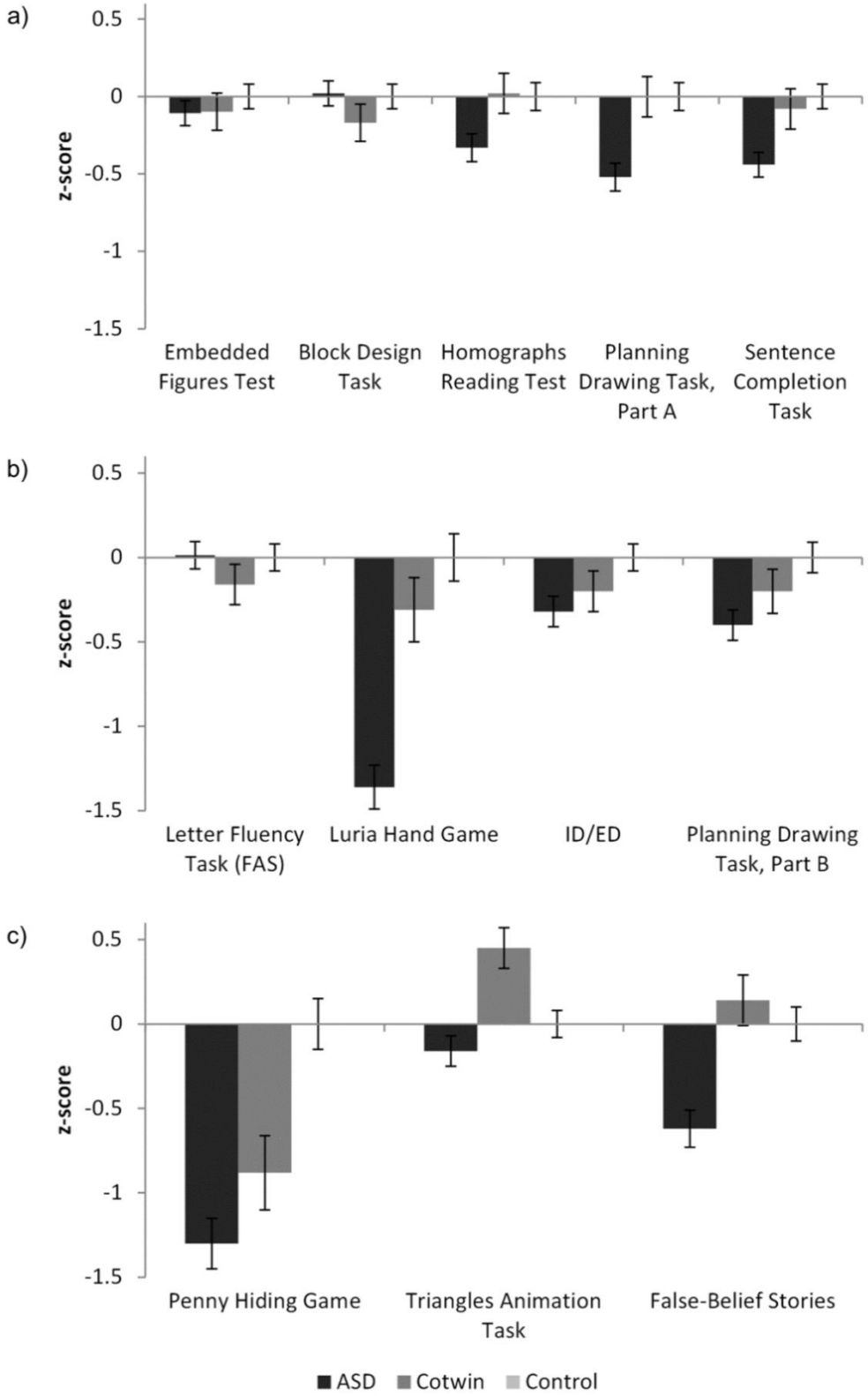


Figure 4.1. Performance on cognitive measures assessing a) central coherence, b) executive function, and c) theory of mind, for all groups after accounting for IQ.

Scores are presented as z-scores relative to the control group. Error bars show standard error.

Due to the heterogeneity in cognitive performance within the ASD group, means may not fully reflect performance across the groups. To compare performance further, frequencies were calculated for atypical performance on each cognitive measure. Atypical performance was defined as one standard deviation above (EFT and Block Design Task only) or below (all other tasks) the control group mean. The number of cognitive tasks on which participants performed atypically is shown in Table 4.4. Results indicated that 63% of individuals with ASD performed atypically in three or more cognitive measures, compared to 31% of unaffected co-twins and 23% of controls. The ASD group performed atypically on significantly more tasks than the unaffected co-twin and control groups; $F(2,385) = 36.28$, $p < .001$, $\eta^2 = .159$; post-hoc Tukey tests *p*s < .001. The unaffected co-twin group and control group did not differ in the number of tasks performed atypically ($p = .279$).

Table 4.4. Number (percentage) of individuals with ASD, their unaffected co-twins, and controls performing atypically on cognitive measures (defined as 1 S.D. above/below the control group mean).

Number of cognitive measures in the atypical range	ASD (*N* = 158)		Unaffected Co-twins (*N* = 71)		Controls (*N* = 159)	
	N	(%)	*N*	(%)	*N*	(%)
0	12	(7.6)	7	(9.9)	19	(11.9)
1	19	(12.0)	16	(22.5)	56	(35.2)
2	27	(17.1)	26	(36.6)	47	(29.6)
3	41	(25.9)	13	(18.3)	25	(15.7)
4	25	(15.8)	6	(8.5)	9	(5.7)
5+	34	(21.5)	3	(4.2)	3	(1.9)

We examined how many individuals showed atypicalities across the cognitive domains, by totalling the number of participants performing one standard deviation above (EFT and Block Design only) or below the mean on at least one measure in each cognitive domain. Figure 4.2 shows how many individuals with ASD, unaffected co-twins and controls had no cognitive atypicalities, single cognitive atypicality, dual cognitive atypicalities, or multiple cognitive

atypicalities. The CC domain showed the highest proportion of individuals with atypical performance solely in that domain, perhaps due to more tasks assessing this aspect of cognition. The most frequently co-occurring cognitive atypicalities were in the CC and EF domains. Furthermore, there was a significant relationship between group (ASD, unaffected co-twin, control) and presence of multiple cognitive atypicalities (X^2 (2) = 41.20, p < .001); the ASD group showed the highest proportion of multiple cognitive atypicalities (32% of ASD group) compared to the unaffected co-twins (11%) and control groups (6%).

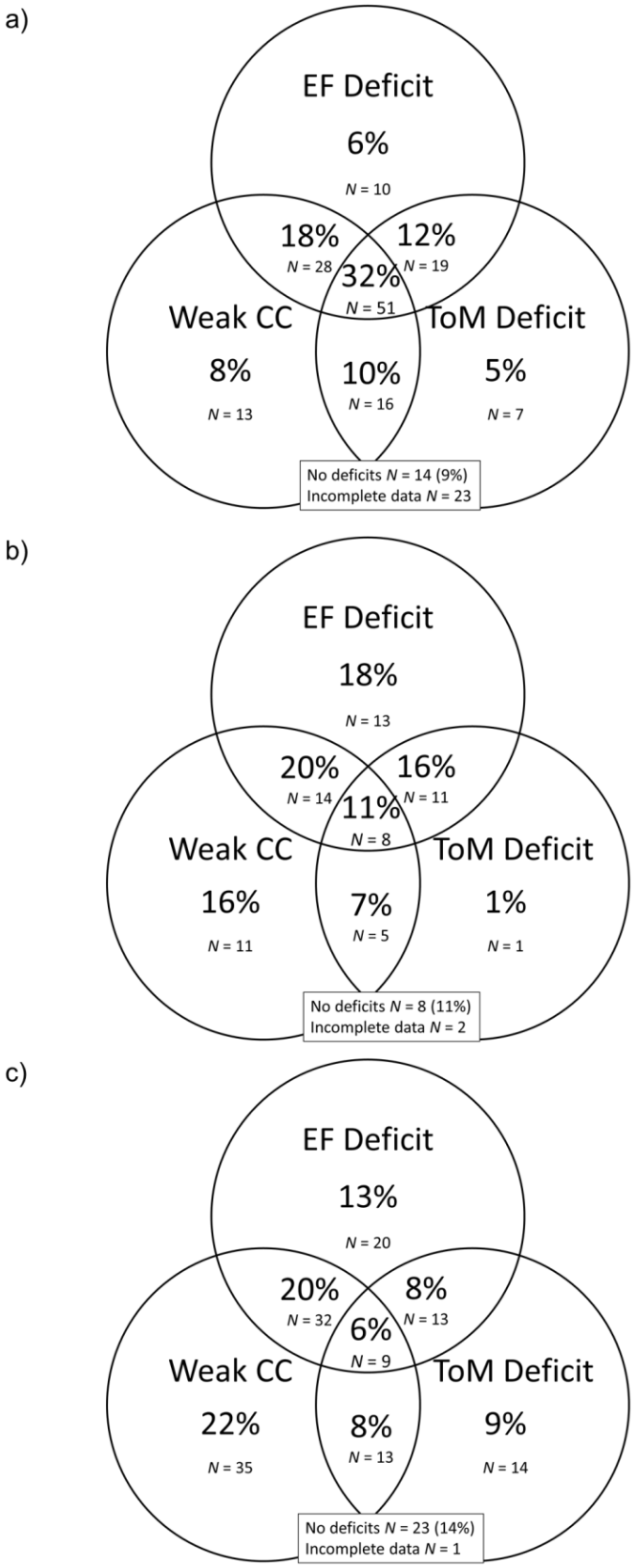


Figure 4.2. Venn diagrams showing the number and percentage of participants a) in the ASD group, b) the unaffected co-twin group, and c) the typically-developing control group, with atypical performance (1 S.D. above/below control group mean) in the three cognitive domains. The central region indicates atypicalities in all three cognitive domains.

In the ASD group, correlation analyses indicated that the number of cognitive atypicalities was related to the severity of ASD symptoms (as measured by ADOS calibrated severity scales [ADOS-CSS]; (Gotham, Pickles, & Lord, 2009), r = .27, p = .001. An ANOVA revealed a significant difference in the severity of ASD symptoms (ADOS-CSS) according to the number of cognitive atypicalities (none, single, dual, multiple), $F(3,153) = 3.39$, p = .020, η^2 = .062, with Tukey post-hoc comparisons indicating significantly more severe symptoms in ASD individuals with multiple atypicalities (M = 6.75) compared to ASD individuals with no cognitive atypicalities (M = 4.50, p = .026).

4.6 Discussion

The aim of this paper was to investigate the pattern of cognitive atypicalities in ASD in a population-based sample to clarify the mixed findings in the literature. Group differences on a cognitive battery devised to assess ToM, EF and CC and the prevalence of multiple cognitive atypicalities were reported for individuals with ASD, their unaffected co-twins, and comparison typically-developing individuals. The patterns of results from the group comparisons are discussed in this section.

The 'weak central coherence' account of ASD suggests that individuals with ASD will be better at tasks where a local processing bias is beneficial, such as the EFT (Happé & Frith, 2006) and Block Design Task (Shah & Frith, 1993). However, in the current study the ASD group did not significantly outperform the unaffected co-twins or the control group on the EFT or on the Block Design Task. This finding is in contrast to previous studies findings of superior performance on the EFT and Block Design Task in adults with ASD (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983) but in line with findings from White and Saldana (2011), who reported that children with ASD performed similarly to typically-developing children on the EFT.

The 'weak central coherence' account of ASD also suggests that individuals with ASD will have poorer performance on tasks which place demands on global processing compared to typically-developing children. In the current study the ASD group performed below the typically-developing control group in all three CC tasks tapping global processing, in support of previous findings that individuals with ASD perform worse than typically-developing individuals on the

Homographs Reading Test (Happé, 1997), Planning Drawing Task (coherence score; Booth, et al., 2003) and the Sentence Completion Task (Booth & Happé, 2010).

In support of the executive dysfunction account, the ASD group performed below the control group in two tasks measuring EF, specifically those purporting to measure cognitive set-shifting (IDED) and planning (Planning Drawing Task, Part B), and below both comparison groups on a test of inhibition (Luria Hand Game). Previous findings have also reported poor performance by children with ASD in the Luria Hand Game (Hughes, 1996), ID/ED (Ozonoff et al., 2004) and the Planning Drawing task (Booth, et al., 2003). No group differences were found for the test of generativity used in the present study (Letter Fluency Task).

The ASD group performed significantly below both comparison groups in the Penny Hiding Game, Triangles Animation Task and the False-Belief Stories. These findings provide additional support for a ToM deficit in ASD.

There was a mixed pattern of results regarding whether the unaffected co-twins of those with ASD shared cognitive features with their affected siblings. The unaffected co-twins outperformed the ASD group in the Sentence Completion Task (CC), Luria Hand Game (EF) and all three ToM tasks. However, on all other cognitive tasks (exception; Penny Hiding Game) the unaffected co-twins were not significantly better than the ASD group, nor significantly worse than the control group, even when significant differences were found between the ASD and control group. This may reflect an intermediate cognitive profile in siblings of those with ASD, or it could be due to a lack of statistical power to detect group differences; this group was approximately half the size of the other two groups. In contrast to the findings of Hughes, Russell, and Robbins (1994), we did not find evidence of EF deficits in siblings of children with ASD, nor did the siblings show weak CC on the present tasks. There was evidence that the broader autism phenotype included ToM deficits, but only in the Penny Hiding Task. It should be noted that the unaffected co-twins in fact performed substantially better in one mentalising task (Triangles Animation Task) than both the ASD and control groups, possibly indicating compensatory skills or protective factors.

The ASD group had a greater number of cognitive deficits/differences overall than both of the other groups. This finding supplements Pellicano (2010a) study, in which children with ASD showed difficulties in false-belief understanding, higher-order planning and cognitive flexibility at

ages 4-7 years and 7-10 years old relative to typically-developing controls. Additionally, in the present study, nearly a third of the adolescents with ASD had multiple cognitive atypicalities, i.e., they had atypical performance in tasks across cognitive domains. Pellicano (2010a) also found that at age 4-7 years, over half of individuals with ASD had multiple cognitive atypicalities, which declined to 19% by age 7-10 years. However, multiple cognitive atypicalities were not exhibited by every individual with ASD, as might be predicted from a strong version of the fractionated triad/multiple deficit account proposed by Happé and Ronald (2008). Instead, multiple cognitive atypicalities seem to be characteristic, but not a universal feature, of ASD.

In this study the individuals with ASD who had multiple cognitive atypicalities also had more severe ASD symptomatology than those with no cognitive atypicalities. As suggested by Happé, Ronald, et al. (2006), this highlights the need to move away from single cognitive accounts of ASD that reduce the behavioural symptoms of the condition to a single underlying cognitive deficit. Instead, a multiple cognitive account of ASD, incorporating several cognitive functions, could provide an explanation for the symptomatology of ASD (Brunsdon & Happé, 2014; Happé & Ronald, 2008; Happé, Ronald, et al., 2006). Previous work has attempted to address whether cognitive atypicalities, either alone or together, are related to the behavioural features of ASD (reviewed in Brunsdon and Happé, 2014). Only a handful of studies have specifically investigated the relationship between test performance in multiple cognitive tasks and the various symptom domains of ASD (Joseph & Tager-Flusberg, 2004; Pellicano, 2013; Pellicano, et al., 2006). Joseph and Tager-Flusberg (2004) reported that much of the relationship between ToM, EF and symptom severity in ASD could be accounted for by language ability. However, ToM ability and higher level EF were directly related to the severity of communication symptoms in ASD, but not to reciprocal social interaction and RRBIs. Contrary to Joseph and Tager-Flusberg's (2004) findings and their own predictions, Pellicano, et al. (2006) found that performance on CC, EF and ToM tasks failed to correlate with any of the three symptom domains in ASD (Pellicano, et al., 2006). In a longitudinal analysis, ToM ability was related to social-communication symptoms, and EF was related to both social-communication symptoms and RRBIs, and CC did not relate to any symptom domains (Pellicano, 2013). Future work is needed to resolve conflicting results and to investigate further whether cognitive atypicalities, either alone or together, are related to the behavioural features of ASD contemporaneously or developmentally.

The SR study has many strengths; it is a large population-based study, with an ASD group that covers the whole ASD spectrum from those with broader spectrum diagnoses through to those who are severely affected, along with a large typically-developing comparison group. As the sample contained siblings (i.e., the unaffected co-twins), it was possible to investigate whether cognitive deficits are part of the broader autism phenotype. The study included a wide range of cognitive tasks as well as IQ, allowing us to establish which group differences in ToM, EF or CC survive correction for differences in general intellectual functioning between the groups.

Several limitations need to be considered when reflecting upon the results of the study. First, some potentially eligible families did not enrol in the SR study, and as such the sample, while population-based, is self-selected. Secondly, the adolescents were approximately 13 years of age when they were tested, but many of the tasks are more commonly used to assess younger children. The task battery was designed to assess a wide range of abilities, given the variability of IQ in the ASD group. However, as a result, many adolescents scored close to ceiling on the Luria Hand Game and False-Belief Stories and close to floor (in error scores) on the Planning Drawing Task and Penny Hiding Game. In principle, floor and ceiling effects constrict range and may therefore mask true group differences. In the present analyses, IQ was regressed out and a transformation applied prior to analysis to reduce skew-ness in the cognitive task data. Our results showed significant group differences even in cognitive tasks that showed some floor/ceiling effects. Thirdly, the tasks may not have fully encapsulated the cognitive ability that they purport to measure, and may not have been equally discriminating across domains. For example, there is no single task/battery that can exhaustively measure all aspects of EF, and tests of individual EFs are rarely “process pure“.

4.6.1 Conclusion

The present results suggest that multiple cognitive atypicalities are characteristic, but not a universal feature, of ASD. Several group differences were found in cognitive tasks that are purported to test CC, EF, and ToM. Analysis of individual performance showed that no one deficit was universal in the ASD group. However, participants with ASD had more cognitive atypicalities overall than either unaffected co-twins or typically-developing control participants. Furthermore, nearly a third of the ASD group had multiple cognitive atypicalities, i.e., they showed atypical performance in CC, EF and ToM. The next step will be to investigate in this

large, population-based sample whether specific cognitive atypicalities, either alone or in combination, are related to specific behaviours characteristic of ASD.

Chapter 5 One or Many: Examining the Relationship Between Different Cognitive Characteristics of Autism Spectrum Disorder

Chapter 5 focuses on one of the predictions of the fractionated theory of ASD posited in Chapter 2; that performance on social and non-social cognitive tasks should be relatively independent. This study investigated the relative in/dependence of three cognitive domains relevant to ASD, using data from 181 adolescents with ASD, 73 of their unaffected co-twins, and 160 controls.

5.1 Introduction

Autism spectrum disorder (ASD) is diagnosed based on deficits in social communication and social interaction, and restricted, repetitive patterns of behaviours and interests (American Psychiatric Association, 2013). The various cognitive theories proposed to explain these behavioural symptoms can be broadly divided into domain-specific and domain-general theories. Domain-specific theories situate the primary deficit in social processing, for example the 'Theory of Mind' (ToM) deficit account (Frith, et al., 1991b). Domain-general accounts of ASD propose that the primary deficit/difference is not specifically in social cognition but lies in, for example, 'executive functions' (EF; Hill, 2004) or superior processing or differences in cognitive style, such as weak central coherence (CC; Happé & Booth, 2008; Happé & Frith, 2006) 'enhanced perceptual processing' (Mottron, et al., 2006), 'systemising' (Baron-Cohen, 2009) and enhanced discrimination (O'Riordan & Plaisted, 2001). This study focuses on the relationship between task performance on cognitive measures purported to assess the three most established cognitive theories; ToM, EF, and CC.

A robust link between ToM and EF in ASD has been widely reported. Positive correlations have been reported between false-belief tasks investigating ToM in children with ASD and tasks measuring various aspects of EF (e.g., Ozonoff, et al., 1991). In addition, Pellicano (2007) reported a significant correlation in an ASD group between a ToM composite and several components of EF (planning, set-shifting, and inhibition), independent of age and IQ. Pellicano's (2007; 2013) findings suggest a developmental relationship between EF and ToM; specifically

that EF is a prerequisite for the development of ToM. In contrast, White (2013) has suggested the 'Triple I impairment' (impairment in 'Inferring Implicit Information') to replace the EF account of ASD. The Triple I impairment suggests that individuals with ASD have difficulties in many experimental tests of EF due to difficulties inferring information about the experimenter's expectations or intentions (i.e., due to poor ToM).

The relationship between CC and cognitive deficits in ASD has been less widely studied and little consensus has emerged. Some studies have found no links between tasks measuring CC and ToM (Happé, 1994a, 1997; Pellicano, et al., 2006). Burnette, et al. (2005) found a link between verbal measures of CC and ToM, but this was no longer significant once IQ was taken into account. Similarly, Pellicano, et al. (2006) found that correlations between performance in ToM and CC measures disappeared once age, verbal ability, and nonverbal ability were accounted for. In contrast, Jarrold, et al. (2000) reported a significant relationship between ToM and CC task performance in ASD.

EF and weak coherence appear to be dissociable (Booth & Happé, 2010; Pellicano, 2010b; Pellicano, et al., 2006). Pellicano, et al. (2006) found that good performance on CC measures was related to better performance on EF tasks in an ASD group, but that correlations were not significant once age and ability were taken into account. In addition, Booth, et al. (2003) compared boys with ASD and those with attention-deficit/hyperactivity disorder (ADHD) on a drawing task examining both cognitive processing style (CC) and planning ability (EF). Poor planning ability did not predict a detail-focussed cognitive style. Booth and Happé (2010) also reported results from a sentence completion test of coherence in the same ASD and ADHD groups. Performance on the CC test and EF test was not significantly correlated and only the ASD group showed a local response style. Research to date therefore suggests that weak coherence is independent of EF.

Finally, Pellicano (2010a; 2010b) conducted the first prospective study to examine the development of multiple cognitive atypicalities in ASD over a three year period. Children with ASD showed difficulties in false-belief understanding, higher-order planning and cognitive flexibility at ages 4-7 years (time 1) and 7-10 years old (time 2) in comparison to typically-developing controls. Principal components analysis at time 1 yielded four factors, with ToM, CC and EF measures falling on separate factors. The EF tasks loaded onto two separate factors;

one which could be interpreted as a 'planning' factor, and the second as a 'shifting/working memory' factor. At time 2, however, only two factors emerged, with the ToM and EF tasks loading together and only the CC measures remaining distinct. Examining predictors of change over time, the pattern of inter-relations indicated that EF and CC emerged as relatively distinct, and ToM and EF showed a significant concurrent (at time 2) and developmental relation.

A relatively recent approach to understanding the deficits seen in ASD is that put forward by the fractionated triad account; a theory in which the social and non-social symptoms of ASD are suggested to have distinct causes at the genetic, neural, cognitive, and behavioural levels (Brunsdon & Happé, 2014; Happé & Ronald, 2008; Happé, Ronald, et al., 2006). This account makes two predictions at the cognitive level; (1) the three areas of cognitive deficits/differences (ToM, EF and CC) should be relatively independent from each other, and (2) the three areas of cognitive deficits/differences should relate differentially to distinct ASD symptoms (Brunsdon & Happé, 2014; Happé & Ronald, 2008). The existing literature pertinent to these two issues was comprehensively reviewed in Chapter 2.

Recent theories that suggest a failure of Bayesian inference in ASD predict that cognitive features (and symptoms) should be inter-related since they attempt to explain all aspects of ASD with a single underlying processing perturbation (Pellicano & Burr, 2012). For example, Davis and Plaisted-Grant (2015) propose that low neural noise is the single cause of cognitive atypicalities in ASD. de Cruys, et al. (2014) postulates that cognitive atypicalities can be explained by an inflexible processing of predictive errors (i.e., violations to expectations) in ASD. In light of the re-emergence of these single deficit models, the current study investigated how much cognitive functions relate to each other, which could help refine these models.

The main focus of the present study was to examine the relative independence of three cognitive functions relevant to ASD in a substantial population-based sample of ASD and comparison twins. The Social Relationships (SR) study provides a suitable basis to investigate the inter-relation between cognitive functions as it focuses on a subset of adolescent twins who meet diagnostic criteria for ASD from the Twins Early Developmental Study (TEDS), and a comparison control group with low ASD traits, obtained from TEDS. All twin pairs within the SR study were administered an extensive cognitive battery to measure IQ, ToM ability (mentalising and false belief understanding), EF (planning, set-shifting, mental initiation, and inhibitory

control), and CC (local and global processing). The first aim was to investigate the underlying structure of this cognitive task battery to create data-driven composites using a factor analytical approach. It was predicted that measures assessing CC would contain two factors; a local processing factor and a global processing factor as Happé and Booth (2008) have suggested that weak CC may itself reflect two separable components that are often confounded in tests; increased local processing and decreased global processing. It was also predicted that there would be a separate EF factor and a separate ToM factor based on Pellicano's (2010b) findings. The second aim was to establish the inter-relation between performance on task batteries devised to assess ToM ability, EF, and CC, in a population-based sample of adolescent twins with ASD, their co-twins, and control twin pairs. The relationship between performance on cognitive composites created from the factor analysis were examined. Based on the prediction from the fractionated account of ASD (Happé & Ronald, 2008), it was expected that performance on composite measures of CC, EF, and ToM would be relatively independent in individuals with ASD once IQ was taken into account.

5.2 Method

5.2.1 Participants

Participants were recruited as part of the SR study (described in Chapter 3). The sample for the current analyses consisted of an ASD group with 158 adolescents (13 years 6 months; 133 males), the unaffected co-twin group with 71 adolescents (13 years 6 months; 27 males) and the control group with 160 adolescents (12 years, 10 months; 110 males). Table 4.1 provides further information regarding the age, IQ, gender, zygosity, ADI and ADOS scores of the ASD, co-twin, and control group. Information regarding the diagnostic classification procedure can be found in Chapter 3. In brief, participants were diagnosed with ASD using diagnostic instruments; the ADI-R (Lord, et al., 1994) and the ADOS (Lord, et al., 2000).

5.2.2 Measures

5.2.2.1 Intellectual Ability.

Intellectual ability was assessed using the WASI (Wechsler, 1999) to obtain an estimated score for IQ. The current study used the Block Design subtest as a measure of CC. Therefore, the

two-subtest version of the WASI (includes Matrix Reasoning and Vocabulary) was used as an estimate of IQ.

5.2.2.2 Cognitive Task Battery

The measures in the cognitive task battery (with the targeted components), key variables, number of trials, and reference to procedure are described in Chapter 3 and are presented in Table 5.1. The cognitive task battery was designed to assess ability across cognitive domains, including CC, EF, and ToM.

Table 5.1. Battery of cognitive measures used in Social Relationship Study (SR) by cognitive domain with references to studies describing task procedure.

Cognitive Measure	Key Variable	Reference for task procedure
Central Coherence		
Embedded Figures Test (EFT)	Accuracy	Shah and Frith (1983)
Block Design Task	Accuracy	Shah and Frith (1993)
Homographs Reading Test	Context effect	Happé (1997)
Planning Drawing Task, Part A	Coherence score	Booth, et al. (2003)
Sentence Completion Task	Error score	Booth and Happé (2010)
Executive Function		
Letter Fluency Task (FAS)	Number of correct responses	Turner (1999)
Luria Hand Game	Conflict score	Hughes (1996)
Intradimensional/Extradimensional Task (ID/ED)	Reversal errors	Hughes, et al. (1994)
Planning Drawing Task, Part B	Planning score	Booth, et al. (2003)
Theory of Mind		
Penny Hiding Game	Error score	Baron-Cohen (1992)
Triangles Animation Task	Mentalising score	Abell, et al. (2000)
False-Belief Stories	First- and second-order false-belief score	Perner, et al. (1989)

5.2.3 Procedure

Home visits were made to all families by two trained researchers. The ASD families completed two home visits, which lasted approximately six hours in total. Twins in the ASD sample completed diagnostic assessments; the ADOS (Lord, et al., 2000) and the ADI (Lord, et al., 1994). The control families completed one home visit, which lasted for approximately two hours. Both the ASD and control families completed an extensive cognitive battery to measure IQ, language ability, CC, EF and ToM ability. The batteries were administered in a counterbalanced order with two fixed orders of tasks. A different experimenter assessed each participant within the twin pair in order to reduce possible experimenter bias.

5.3 Results

All twins were treated as singletons in the analyses to allow comparisons between groups of adolescents with ASD (termed ASD group), unaffected co-twins, and a control group. Reaction time in EFT, total error score in the Sentence Completion Task, the coherence score and planning score from the Planning Drawing Task, reversal errors in ID/ED, and error score for the Penny Hiding Game were reflected so that a higher score indicated better performance in all tasks. The cognitive task data did not meet assumptions of a normal distribution, with skew and kurtosis present in most of the cognitive variables. All variables were normalised using a Van der Waerden transformation. To account for IQ, standardised residuals for the ASD and co-twin group were obtained from the regression line fit when fitting each factor score as a dependent variable in a linear model with IQ as a predictor variable, according to the control group (Thomas et al., 2009).

5.3.1 Exploratory Factor Analysis

A principal axis factor (PAF) was used to examine the underlying constructs in the cognitive data using an oblique rotation as it permits correlations between factors. Twelve transformed variables were analysed (EFT score was excluded as it was non-orthogonal, related, and dependent on EFT reaction time. Results were the same for either variable). The two scores from Planning Drawing Task (Part A& B) were entered together as the two scores are orthogonal, independent measures. The correlation matrix was analysed and an oblimin rotation was applied to obtain oblique (correlated) factors. An examination of the Kaiser-Meyer-Olkin

(KMO) measure of sampling adequacy suggested that the sample was factorable (KMO = .66) (Hair, Anderson, Black, & Tatham, 1984). Bartlett's Test of Sphericity was significant; $\chi^2(66) = 234.23$, $p < .001$. Kaiser (1960) criterion and Cattell (1966) "scree test" were used to determine the number of factors to extract. An eigenvalue of 1 indicated that four factors were to be retained (see Appendix 2).

Only items with a loading above .30 were considered relevant to the factor loadings. The results of the oblique rotation of the solution are shown in Table 5.2. Together, these four factors explained a total of 47% of the variance for the entire set of variables. The first factor contained three items with the highest loadings from two cognitive measures designed to measure the ability to process stimuli locally and so was termed 'local processing factor' and explained 16% of the variance. The second factor contained three items with the highest loadings from cognitive tasks designed to measure EF and so was termed 'EF factor' and explained a further 13% of the variance. The third and fourth factors were each composed of a single measure. The third factor explained a further 9% of the variance and was composed of a ToM measure and so was termed 'ToM factor'. The fourth factor was composed of a measure designed to assess the ability to process stimuli globally and so was termed 'global processing factor'. This factor explained a further 9% of the variance.

A confirmatory factor analysis (CFA) was conducted on the 4 factor solution separately for ASD and control groups to test the relative model fit. The CFA for the control group showed acceptable model fit ($\chi^2 = 21.18$, df = 18, $p = .271$, RMSEA = .033, CFI = .952, AIC = 3490.062). The CFA for the ASD group did not show acceptable model fit ($\chi^2 = 36.23$, df = 18, $p = .007$, RMSEA = .081, CFI = .727, AIC = 3738.612). The Tucker's coefficient of congruence across the ASD and control groups ranged from high for the first factor (.90), medium for the second and fourth factor (.61/.54), and low for the third factor (.13). This indicates that the factor structure is largely different between the ASD and control group, and there is high factor similarity for the first factor across the two groups.

Table 5.2. Cognitive measures loading on four factors extracted using principal axis factoring with an oblimin rotation.

Factor 1 Local processing factor		Factor 2 EF factor		Factor 3 ToM factor		Factor 4 Global processing factor	
Items	Loadings	Items	Loadings	Items	Loadings	Items	Loadings
EFT[CC]†	.66	Luria Hand Game[EF]	.58	False-Belief Stories[ToM]	.57	Planning Drawing A (coherence)[CC]†	.38
Block Design Task[CC]	.65	ID/ED[EF]†	.45				
Triangles Animation Task[ToM]	.43	Planning Drawing B (planning)[EF]†	.33				

Abbreviations: [CC]=central coherence measure, [EF]=executive function measure, [ToM]=theory of mind measure, †reversed scored

The factor loadings were then used to create overall factor scores. A factor score was saved for each participant in relation to each identified factor (Table 5.2). Four separate factor scores were calculated by multiplying the factor loading by the item score for each item identified to be relevant to each factor before averaging to gain unit-weighted factors. Figure 5.1 shows the means for the factor scores across groups, including significant mean differences between groups (ASD, unaffected co-twins, controls).

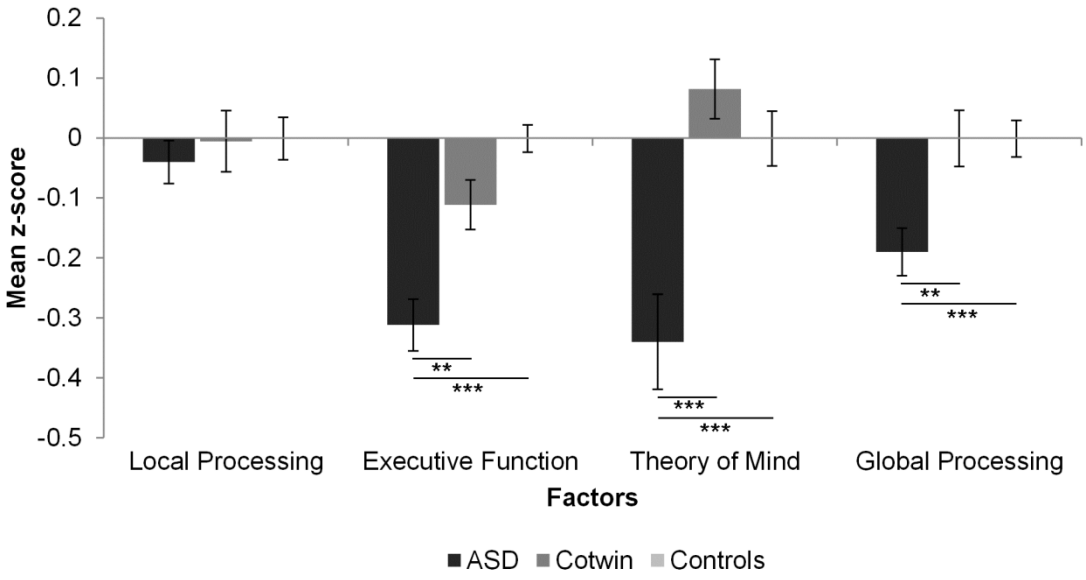


Figure 5.1. Means and group differences for unit-weighted factor scores (adjusted for IQ) for ASD and unaffected co-twins, relative to the control group.

Note: Error bars show standard error. Group differences were conducted using ANOVA and Tukey post-hoc analyses test with alpha of .05, $^{**}p < .01$, $^{***}p < .001$.

The relationship between the factor scores was then examined using Pearson's correlational analyses, with the correlation coefficients presented in Table 5.3. All correlations between the factor scores were non-significant in the unaffected co-twin group (highest r = -.22, lowest p = .073). There was a significant negative correlation between the EF and global processing factors in the control group. The correlation coefficients were not statistically different across the co-twin and control comparison groups (Zs < 1.89, ps > .059). In the ASD group, the local processing factor was not correlated with any other factor, but the ToM factor was correlated with the EF and the global processing factors. In addition, these significant correlation coefficients were significantly different to the control group (all Zs > 3.01, all ps < .003), but not significantly different to the co-twin group. In addition, the correlation between EF and the global processing factors was significantly different between the control and ASD groups (Z = 2.28, p = .023).

Table 5.3. Pearson's correlations between unit-weighted factor scores (adjusted for IQ) for ASD, unaffected co-twins, and control groups.

Group	Factors	1	2	3	4
ASD	1. Local Processing Factor	-			
	2. EF Factor	.06	-		
	3. ToM Factor	.07	.22*	-	
	4. Global Processing Factor	.15	.15	.29***	-
Controls	1. Local Processing Factor	-			
	2. EF Factor	.01	-		
	3. ToM Factor	.08	-.03	-	
	4. Global Processing Factor	.03	-.15	-.07	-
Unaffected Co-twins	1. Local Processing Factor	-			
	2. EF Factor	-.01	-		
	3. ToM Factor	.06	-.05	-	
	4. Global Processing Factor	.02	-.19*	-.07	-

Note:$p < .05$, **$p < .01$, ***$p < .001$.

5.4 Discussion

5.4.1 Summary of Findings

The main aim of the current chapter was to establish the inter-relation between performance on task batteries devised to assess CC, EF and ToM. A factor analytical approach was used to investigate the underlying structure of the cognitive tasks to create data-driven composites. This suggested that the cognitive battery could be reduced to four factors; two factors relating most closely to the concept of CC, one factor relating to ToM, and one factor relating mostly to EF. The relationship between these four factors was investigated and it was found that in the ASD group; (1) ToM and EF factors were correlated, and (2) ToM and global processing factors were correlated. No significant relationships between factors were found in the typically-developing control group or the co-twin group. Thus only partial support was given to the fractionated triad account.

The study revealed a two-factor structure to the CC measures; a local processing factor and a global factor emerged. The local-processing factor contained performance on the EFT, Block Design Task and the Triangles Animation Task; as such it may reflect individuals' local processing abilities or more general visuo-spatial abilities. The CC measures designed to capture global or contextual processing did not load together on a single factor. Instead, the global processing factor contained only performance on the Planning Drawing Task, Part A – a measure of coherence. It could be suggested that these tasks did not optimally tap the CC ability they were purported to measure. For example, the Homographs Reading Test and the Sentence Completion Task require integrative processing but also, arguably, inhibitory control, i.e., participants needs to inhibit the more frequent pronunciation to produce an accurate response. In the present analyses, however, these tasks did not load clearly on global CC or EF. Pellicano, Maybery, and Durkin (2005) investigated the convergent validity of visuo-spatial coherence tasks in typically-developing young children. As in the current study, the CC tasks were not highly inter-correlated. Overall, it seems that performance on the three measures of global processing was not driven by a single underlying global processing factor in the present sample.

Van der Hallen, Evers, Brewaeys, Van den Noortgate, and Wagemans (2015) conducted the first meta-analysis of studies of local-global processing in ASD. The meta-analysis examined 56 studies including 1,000 ASD individuals and found preserved local processing in ASD, in line with the current study. In addition, there were no reliable group differences for global processing ability, although there was evidence of slow global processing in ASD. This is in contrast to the current study in which a deficit in global processing was found. The present global processing factor was composed of the coherence score from the Planning and Drawing Task, which would not obviously be influenced by temporal effects. Overall, the meta-analysis seriously challenged the local-global processing concept. In contrast to Van der Hallen, et al. (2015) proposals, we did find evidence of a differentiation between performance in tasks purporting to assess local or global processing. However, not all of the tasks purported to measure global processing loaded together in the factor analysis, which is perhaps problematic for the construct validity of local-global processing. This emphasises the issue highlighted by the meta-analysis that 'local' and 'global' processing need to be more thoroughly conceptualised.

In addition, the factor analysis suggested an EF factor and a ToM factor. The EF factor contained three out of the four tasks designed to tap EF; Luria Hand Game, ID/ED, Planning Drawing, Part B (planning). The ToM factor only contained the False-Belief Stories, suggesting that the tasks designed to tap ToM may investigate different aspects of ToM. However, it needs to be pointed out that the four factors identified only explained 48% of the variance in the data. This could suggest that the cognitive battery was not comprehensive enough and future work should include other factors, such as attention and memory, to account for this unexplained variance.

The current study tested the hypothesis that CC, EF, and ToM would be largely independent. This hypothesis was supported within the control group and the unaffected co-twin group, where there were no significant correlations between cognitive factors, suggesting that cognitive functions are fractionated by adolescence in typical development. Furthermore, the factor analysis specified four factors that could be attributed largely to distinct cognitive functions. However, two significant correlations were reported in the ASD group; 1) ToM and EF, and 2) ToM and global processing. This raises the possibility that the differentiation of specific cognitive functions does not apply in ASD as it does in typical development. Consequently, certain cognitive functions may remain or become inter-dependent in adolescents with ASD.

The fractionated autism triad account at the cognitive level predicts that cognitive functions will be fractionated in ASD (Brunsdon & Happé, 2014). Brunsdon and Happé (2014) reviewed the literature and found that, contrary to predictions of the account, ToM and EF appear to be linked in ASD, although CC seems to be independent. With regards to the first correlation, a link between ToM and EF may reflect similar demands across the tasks. For example, false-belief tasks may require inhibitory control to resist answering with what they currently know to be true to reason about another's belief. In addition, the Luria Hand Game may reflect an aspect of ToM as the child must understand another person's intentions to produce the opposite action to that person. (Pellicano, 2007) suggested that developments in EF are essential for ToM understanding. Therefore, impairment in EF in ASD may hinder false-belief understanding. Due to the nature of the current results, it is only possible to suggest that features of EF, such as inhibition, set-shifting, and planning, are related to performance on tasks assessing false-belief understanding.

As previously mentioned, the fractionated autism triad account predicts that CC will be distinct from other cognitive functions (Chapter 2). However, this study found a relationship between global processing and ToM. In the review of the literature, Chapter 2 found that many studies have not considered that weak CC reflects two separable components when investigating the relationship between cognitive functions. In regards to the results of the current study, a relationship between global processing and ToM raises the possibility that superior eye for detail (as assessed in the local processing factor) is unrelated to ToM, but reduced integration of information in context (as assessed in the global processing factor) may have a detrimental impact on understanding social situations and accurately ascribing mental states in ASD, as suggested in Chapter 2.

The fractionated triad account proposes that cognitive functions should be fractionated in ASD; a prediction that was not entirely supported in the current study. However, the fractionable theory also recognises that any relationships between cognitive functions may also reflect an individual's compensatory skills, which could involve measurable factors (e.g., IQ and language), but they may also reflect differences in environment, intervention, memory, or attention (Chapter 2). This might provide one explanation for the associations found between ToM and EF and global processing and ToM. Further work to disentangle the confounding effects that are found across cognitive functions is needed to provide additional support for the fractionated triad theory of ASD. The current study did account for IQ, but could not account for the effects of memory and attention as the SR study did not include measures of these abilities.

In addition, these correlations may not reflect a causal relationship between different aspects of cognition in ASD, but may instead indicate a co-occurrence of deficits as shown in the pattern of prevalence of cognitive deficits (Chapter 4). This would be predicted by the accounts that predict failure of Bayesian inference in ASD (Davis & Plaisted-Grant, 2015; de Cruys, et al., 2014; Pellicano & Burr, 2012). The correlations could also reflect similar demands across tasks as cognitive tests are rarely 'process pure'. Another explanation of the correlations may be that there are true associations between these cognitive factors, but it is difficult to imply causation or direction of the relationship from correlational analyses (Rutter, 2007).

5.4.2 Strengths and Limitations

The SR study has many strengths; it is a large population-based study, with an ASD group that covers the whole ASD spectrum from those with broader spectrum diagnoses through to those who are severely affected, along with a large typically-developing comparison group. A few limitations of the current study warrant discussion. Firstly, some potentially eligible families did not enrol in the SR study, and as such the sample, while population-based, is self-selected. Secondly, as previously mentioned, the findings cannot imply the direction of causation in the correlational analyses. Thirdly, the children were approximately 13 years of age when they were tested, which is considerably older than previous studies assessing the relationship between cognitive functions in ASD making it difficult to compare our findings directly. Also, the cognitive tasks used in the battery are more commonly used to test much younger children. The task battery was designed to assess a wide range of abilities, given the variability of IQ in the ASD group. As a result, many adolescents scored close to ceiling on the Luria Hand Game and False-Belief Stories and close to floor (in error scores) on the Planning Drawing Task and Penny Hiding Game. In the present analyses, IQ was regressed out and a transformation applied prior to analysis to reduce skewness in the cognitive task data. Finally, the cognitive tasks may not have assessed the cognitive ability they were selected to measure. For example, it should be noted that EF is an umbrella term, covering a diverse set of abilities, and as such, no battery can fully encapsulate all aspects of EF.

5.4.3 Conclusion

This exploratory study aimed to investigate the underlying structure of several cognitive tasks and to explore the inter-relationship between cognitive factors. The factor analysis indicated that the cognitive task battery consisted of four underlying structures; two relating to the concept of CC, one relating to ToM, and one relating to EF. In addition, ToM and EF, and ToM and global processing may be linked at the phenotypic level in ASD, in contrast to the fractionated account of ASD. In typically-developing individuals and unaffected co-twins, the cognitive domains were not significantly related, supporting the fractionated triad account. However, this study was conducted at one time point in adolescence, and so neither the developmental effects of cognitive functions, nor the causal relations, could be examined. Further research is required to examine the relative fractionation of the cognitive functions across development.

Chapter 6 Relations Between Cognitive Deficits and Behavioural Symptoms in Autism Spectrum Disorder

The fractionated triad theory of autism suggests that different cognitive functions may underlie the distinct symptom domains of ASD (Happé & Ronald, 2008). Chapter 2 introduced two predictions of the fractionated theory of ASD at the cognitive level. The prediction that the three areas of cognitive deficit/difference should be relatively independent was investigated in Chapter 5. The present chapter explores the second prediction of the fractionated triad; that the three areas of cognitive deficit/difference should relate differentially to distinct ASD symptoms. The relationship between cognitive task performance and ASD symptomatology is examined in 181 adolescents with a diagnosis of ASD using a structural equation modelling approach which takes the factor structure found in Chapter 5 as a starting point.

6.1 Introduction

Autism has for many years been behaviourally diagnosed on the basis of the characteristic 'triad' of impairments; social impairments, communicative impairments, and restricted and repetitive behaviours and interests (RRBIs) (World Health Organisation, 1992). Although the latest edition of DSM-5 (American Psychiatric Association, 2013) collapses social and communication symptoms into one domain, impairments across the three areas of the triad are still required for a diagnosis of 'Autism Spectrum Disorder'. It has been suggested that the three impairments of the autism triad are 'fractionable', with largely independent causes at the cognitive level (Happé & Ronald, 2008). The current chapter investigates this proposal by investigating the relationship between specific cognitive deficits/differences and the behavioural symptoms of ASD.

A range of cognitive accounts have been proposed to explain the symptoms of ASD, with much focus on three key cognitive theories; a deficit in Theory of Mind (ToM), executive dysfunction (see Hill, 2004, for a review), and weak CC (Frith, 1989; Happé & Booth, 2008). The ToM deficit account suggests that individuals with ASD are unable to reflect on their own and other peoples' thoughts, beliefs, desires and intentions, and has been proposed as a core and universal abnormality in ASD (Baron-Cohen, 1995). The executive dysfunction account of ASD involves

difficulties in planning, inhibition, mental flexibility, and initiation and monitoring of tasks (Hill, 2004). The weak CC account of ASD proposes that individuals with ASD have a processing bias for local details and fail to perceive the global picture (Frith, 1989). The CC account has more recently been modified with an emphasis on a different cognitive style, rather than a deficit, in which individuals with ASD have superior processing of details and a decreased tendency to integrate information (Happé & Booth, 2008).

It is questionable whether any of these cognitive theories can account for the full triad of diagnostic impairments of ASD, let alone the associated features such as raised incidence of talents and uneven cognitive profile. For example, the ToM deficit account posits a primary deficit in the social domain and offers a good explanation for the social interaction deficits in ASD as an impaired ability to represent mental states of oneself and others' could limit social interactions. Furthermore, the ToM account can provide an explanation of the social communication impairments in ASD as successful communication involves recognising the communicator's intended meaning. However, the ToM deficit account struggles to explain the non-social features of ASD, such as RRBIs, motor difficulties, sensory abnormalities and savant skills. Conversely, non-social cognitive accounts of ASD, such as executive dysfunction and weak CC, provide a good explanation for the non-social characteristics of ASD. For example, executive dysfunction in ASD may underlie RRBIs due to a failure to generate new behaviours or shift set. Additionally, a detail-focused cognitive style (as suggested by the weak CC account) may provide an explanation for a specific set of non-social features, such as 'insistence on sameness', narrow special interests and high rates of talent in ASD.

The fractionated triad theory of autism suggests that different cognitive functions may underlie the distinct symptom domains of ASD (Happé & Ronald, 2008). The fractionated theory predicts that performance on, for example, ToM tests should relate most strongly to social-communicative symptoms, while executive dysfunction tests may relate most strongly to RRBIs, and CC tests may relate specifically to uneven cognitive profile, talents and narrow interests. However, surprisingly few studies have considered different cognitive deficits and their relation to the behavioural symptoms of ASD. Studies examining the links between cognition and behaviour in ASD, and specifically those relevant to the differential links prediction of the fractionable triad hypothesis, were reviewed in Chapter 2 and are briefly summarised here.

Only a handful of studies have specifically investigated the relation between test performance in tasks assessing all three cognitive domains (ToM, EF, and CC), and distinct symptom domains in individuals with ASD. Joseph and Tager-Flusberg (2004) used the ADOS to measure symptom severity in children with ASD, and a battery of cognitive tasks to measure ToM and EF. Limited relationships were found between the two cognitive domains and symptom severity in ASD, and relationships could largely be accounted for by language ability. However, ToM ability and higher-level EF were significantly related to the severity of communication symptoms, but not social interaction and RRBIs, in ASD. Pellicano, et al. (2006) used the ADI-R as a measure of symptom severity, and administered a battery of cognitive tasks to measure ToM, EF, and CC in children with ASD. Contrary to Joseph and Tager-Flusberg's (2004) findings and their own predictions, the three cognitive accounts failed to correlate with any of the three symptom domains of ASD.

Taking a longitudinal approach, Pellicano (2013) examined whether early cognitive atypicalities at age 4 to 7 years could predict later behavioural symptoms of ASD, as measured by the ADOS and Repetitive Behaviour Questionnaire at a 3-year follow-up. ToM ability (specifically false-belief understanding) was related to social-communication symptoms, and EF (planning ability, cognitive flexibility, inhibitory control) was strongly related to both social-communication symptoms and repetitive behaviours. Specifically, early EF but not ToM ability predicted the degree of social-communication impairments and repetitive behaviours, highlighting the critical role of early EF development in influencing the behavioural symptoms of ASD. There was no correlation between early CC (local processing) and later behavioural symptoms of ASD, nor predictive relationship between early CC and later insistence on sameness. This recent study conflicts with the fractionable triad account as different cognitive functions were not found to be uniquely related to the distinct symptom domains of ASD.

The current study investigated the prediction from the fractionated triad account that specific cognitive deficits will relate differentially to specific symptom domains in ASD. The Social Relationship (SR) study provides an opportunity to investigate the relationship between cognitive functions and behavioural symptoms in a population-based sample of adolescent twins who meet diagnostic criteria for ASD. All twin pairs within SR study were administered an extensive cognitive battery to measure IQ, language ability, ToM ability (mentalising and false belief), EF (planning, mental flexibility, mental initiation, and inhibitory control), and CC (local

and global processing). The twins suspected of having ASD were also behaviourally assessed for ASD symptomatology in the three symptom domains using parent report of past and current functioning (ADI-R) and direct observation (ADOS).

The main aim of the current analyses was to investigate the differential relationship of test performance on CC, EF, and ToM tasks with the symptom domains of ASD using a structural equation modelling approach. Analyses relevant to this aim were based on data from the ASD participants only, since the control group (selected for low ASD traits; see Chapter 3) did not complete symptom measures. In addition, the unaffected co-twins of those with ASD were not included in the analyses due to relatively small numbers and hence limited statistical power.

The inter-relationship among cognitive tasks designed to assess EF, CC and ToM in the SR study sample was explored in Chapter 5. The exploratory factor analysis revealed a four factor solution to the cognitive measures; two factors relating most closely to the concept of central coherence (CC), one factor relating to theory of mind (ToM), and one factor relating mainly to executive function (EF). The results of the exploratory factor analysis informed the confirmatory factor analysis and structural equation models that were used here to investigate the relationship between cognitive domains and ASD symptomatology. The ADI-R and ADOS domain scores based on diagnostic algorithms were used as measures of the level of impairment on each part of the autism triad with a higher score indicating increased symptom severity. It was predicted that test performance on a ToM factor would relate to social and communication symptoms and test performance on an EF factor would relate to RRBI symptoms. Since we distinguish local and global processing, it was predicted that global processing would impact on communication (Noens & van Berckelaer-Onnes, 2004; Noens & van Berckelaer-Onnes, 2005) and good local processing would not be disadvantageous to ASD symptoms given previous findings (e.g., Burnette, et al., 2005; Drake, et al., 2010; Loth, et al., 2010; Pellicano, 2013; South, et al., 2007)

6.2 Method

6.2.1 Participants

The individuals with ASD were recruited as part of the SR study (described in Chapter 3). In the current analyses, the ASD group contained 181 adolescents diagnosed with ASD based on

information from the ADOS and ADI-R, with consensus diagnosis reached between trained clinicians. Individuals were between 12 and 16 years old (*M* = 13.5-years-old) and the group comprised 150 males and 31 females. Participant characteristics are shown in Table 6.1.

Table 6.1. Participant characteristics

	ASD			
	N	*M*	*(SD)*	Range
Age (years)	181	13.49	(0.69)	12.08-16.25
IQ (WASI 2-subtest)	153	94.07	(16.91)	55-128
IQ (imputed score)	181	90.02	(20.34)	49-128
ADOS total (raw)†	174	11.38	(6.14)	0-26
ADI total†	177	37.64	(16.19)	3-70
Gender	150 Males/31 Females			
Zygosity	51MZ/130DZ			

Note: †higher score = more severe

Abbreviations: ASD = autism spectrum disorder; DZ = dizygotic twin pairs; M = mean average; MZ = monozygotic pairs; N = number of participants; SD = standard deviation; TD = typically-developing controls.

6.2.2 Measures

The measures used in the current analyses are described fully in Chapter 3. All participants completed a cognitive task battery shown in Table 6.2. The cognitive task battery was designed to assess ability across cognitive domains, including CC, EF, and ToM.

Table 6.2. Battery of cognitive measures used in Social Relationship Study (SR) by cognitive domain with references to studies describing task procedure.

Cognitive Measure	Key Variable	Reference for task procedure
Central Coherence		
Embedded Figures Test (EFT)	Accuracy	Shah and Frith (1983)
Block Design Task	Accuracy	Shah and Frith (1993)
Homographs Reading Test	Context effect	Happé (1997)
Planning Drawing Task, Part A	Coherence score	Booth, et al. (2003)
Sentence Completion Task	Error score	Booth and Happé (2010)
Executive Function		
Letter Fluency Task (FAS)	Number of correct responses	Turner (1999)
Luria Hand Game	Conflict score	Hughes (1996)
Intradimensional/Extradimensional Task (ID/ED)	Reversal errors	Hughes, et al. (1994)
Planning Drawing Task, Part B	Planning score	Booth, et al. (2003)
Theory of Mind		
Penny Hiding Game	Error score	Baron-Cohen (1992)
Triangles Animation Task	Mentalising score	Abell, et al. (2000)
False-Belief Stories	First- and second-order false-belief score	Perner, et al. (1989)

6.2.3 Diagnostic Assessments

6.2.3.1 Autism Diagnostic Observation Schedule (ADOS)

The ADOS (Lord, et al., 2000) is a semi-structured observational assessment and is considered a gold-standardised diagnostic tool for assessing ASD. A trained examiner observed the child's behaviour in a series of social events. The behaviour was then coded and the dependent variables used were the communication total score and the social interaction score from the diagnostic algorithm. The communication total score was calculated from four items with a potential score of 0 – 8, the social interaction total score was calculated from seven items with a

potential score of 0 – 14. A RRBI score was calculated from four repetitive behaviour items, with a potential score of 0 – 8.

6.2.3.2 Autism Diagnostic Interview-Revised (ADI-R)

The ADI-R (Lord, et al., 1994) is a standardised assessment tool conducted as a semi-structured parent interview and provides a thorough assessment for ASD. It assesses the developmental history and current behaviour of the individual being evaluated and focuses on three main aspects; language/communication, reciprocal social interaction, and RRBIs. The items were scored from 0 (no impairment) to 3 (severe impairment) and scoring algorithms were used to create three different totals in communication, social interaction and RRBIs.

6.2.4 Procedure

Home visits were made to all families by two trained researchers. The ASD families completed two home visits, which lasted approximately six hours in total. Participants completed gold standard diagnostic assessments; the ADOS (Lord et al. 2000) and the ADI-R (Lord, Rutter and Lecouteur 1994). The participants also completed an extensive cognitive battery to measure IQ, language ability, CC, EF and ToM ability. One of two fixed orders of tasks was completed. A different experimenter assessed each participant within the twin pair in order to reduce possible experimenter bias.

6.2.5 Analyses

The coherence score and planning score from the Planning Drawing Task, reversal errors in ID/ED, and error score in Penny Hiding Game were reflected so that a higher score indicated better performance in all tasks. Furthermore, IQ was found to be related to performance on all of the cognitive measures (all *r*s .16 - .74, all *p*s < .023) and so covariate-adjusted residuals for IQ were used in all further analyses to correct for the effects of IQ.

Confirmatory factor analysis (CFA) and structural equation modelling (SEM) was conducted for those diagnosed with ASD only using Mplus version 7 with maximum likelihood robust estimation (Muthén & Muthén, 1998-2011). This type of estimation produces robust standard errors with non-normal data. Model fit was evaluated using Brown (2006) three recommended criteria: comparative fit index (CFI) ≥ .90, Tucker–Lewis index (TLI) ≥ .90, and root mean square

error of approximation (RMSEA) ≤ .08. CFA was used to index cognitive domains. SEM was used to assess whether there was a relationship between individual differences in performance in cognitive domains and on symptom domains for individuals with a diagnosis of ASD. The models accounted for the non-independence of the twin data by specifying the clustering command, and so adjusted the standard errors accordingly. Two models are reported; the first SEM model for symptoms measured by the ADI-R and the second SEM model for symptoms measured by the ADOS. Based on power calculations (Westland, 2010), the recommended number of individuals is 152 to detect an effect (effect size = 0.1, statistical power level = 0.8, latent variables = 2, observed variables = 5, alpha = .05).

6.3 Results

6.3.1 Confirmatory Factor Analysis

To inform SEM models, CFA was conducted to examine the hypothesis that performance in EFT, Block Design and Triangles Animation task belong to a single factor (termed 'local processing'), and performance in Luria's Hand Game, ID/ED, and Planning score on the Planning/Drawing Task belong to a second factor (termed 'executive function') (based on previous analyses conducted on this data set; see Chapter 5). The chi-square goodness-of-fit was not significant, $X^2(8) = 10.36$, $p = .241$, indicating that the proposed model fitted the data. Furthermore, the model fit indices indicated good model fit, CFI = .99, TFI = .98, RMSEA = .04. Table 6.3 shows the results of the CFA. Individual item loadings ranged from .75 to .92 (all *p*s < .001). The observed variables explained significant variance in the latent factors (R_2 = .56 - .85, all *p*s < .001).

Table 6.3. Standardised coefficients for the Confirmatory Factor Analysis (CFA) for cognitive measures

Observed variable	Latent Variable	β^a	*S.E.*	R^2
EFT	Local processing	0.87	.05	.76
Block Design Task	Local processing	0.91	.04	.83
Triangles Animation Task	Local processing	0.75	.06	.56
Luria Hand Game	Executive function	0.75	.06	.68
ID/ED	Executive function	0.82	.07	.85
Planning Drawing B (planning)	Executive function	0.92	.04	.56

Abbreviations: [a]all significant at $p < .001$. β= standardised coefficient; CFA = confirmatory factor analysis; *S.E.* = robust standard errors.

Note: All β^a and R^2significant at $p < .001$ for all variables.

6.3.2 Structural Equation Models

The ADI-R and ADOS symptom domains were used to index the behavioural symptoms of ASD. The equivalent domain (social, communication, RRBI) and total scores were significantly correlated across the ADI-R and ADOS (lowest $r = .31$-$.47$, highest $p < .001$).

6.3.2.1 ADI-R Model

An SEM analysis was performed based on the 181 individuals with ASD. Included in the model were two latent factors and two observed variables to index the cognitive domains. The two latent factors were based on the CFA model described above. Covariance between the two latent factors was specified. The two observed variables (single tasks falling on the other 'factors', named 'Global' and 'ToM') were the Planning Drawing A (coherence) and False-Belief Stories. The symptom domains as measured using the diagnostic algorithms from the ADI-R were regressed onto the indices of the cognitive domains. The covariance between the symptom domains was specified. The covariance between all cognitive domains was specified.

The chi-square goodness-of-fit was significant, $X^2(28) = 42.72$, $p = .037$, indicating that the proposed model did not fit the data. Modification indices specified that a covariance between EFT and ID/ED be added to the model. The chi-square goodness-of-fit was not significant,

$X^2(27) = 34.55$, $p = .151$, indicating that the proposed model did fit the data. The model fit indices indicated good model fit, CFI = .98, TFI = .98, RMSEA = .04.

Figure 6.1 shows the results of the final hypothesised SEM model and Table 6.4 presents the path coefficients for the model. The two latent factors were correlated, $r = .46$, $p = .013$. False-Belief Stories performance was significantly related to the EF latent factor, $r = .51$, $p < .001$, but was not correlated with the local processing factor, $r = .18$, $p = .243$. Planning Drawing A (coherence) was related to False-Belief Stories performance, $r = .36$, $p < .001$, and both the EF latent factor, $r = .39$, $p = .008$, and the local processing factor, $r = .29$, $p = .010$. Furthermore, significant correlations between all symptom domains were found, all rs > .62, all ps < .001.

The relationship between cognitive and symptom domains was explored (Table 6.4). Both the EF and local processing factors were related to ADI-R communication symptoms and the local processing factor was related to ADI-R social symptoms. All other relationships between cognitive domains and symptom domains were not significant (all ps > .084). The model explained significant variation in ADI-R communication ($R^2 = .27$, $p = .007$) and ADI-R social ($R^2 = .27$, $p = .028$), but not ADI-R RRBIs ($R^2 = .12$, $p = .138$).

6.3.2.2 ADOS Model

An SEM analysis was performed based on 174 individuals with ASD. The model was the same as the previously described SEM, with the exception that the symptom domains were measured by the ADOS (based on the diagnostic algorithm).

The chi-square goodness-of-fit was significant, $X^2(30) = 61.87$, $p < .001$, indicating that the proposed model did not fit the data. The modification indices specified that covariance between EFT and ID/ED, and between the planning score and coherence score on the Planning Drawing task be added to the model. The resulting chi-square goodness-of-fit was not significant, $X^2(27) = 41.01$, $p = .051$, indicating that the modified model did fit the data. The model fit indices indicated good model fit, CFI = .94, TFI = .90, RMSEA = .06.

Figure 6.1 shows the results of the final hypothesised SEM model and Table 6.4 presents the path coefficients for the model. The two latent factors were correlated, $r = .46$, $p = .011$. False-Belief Stories performance was correlated with the EF latent factor, $r = .46$, $p = .001$, but was not correlated with the local processing factor, $r = .21$, $p = .174$. Planning Drawing A

(coherence) was significantly correlated with False-Belief stories performance, $r = .35$, $p < .001$, and the local processing factor, $r = .26$, $p = .041$, but was not correlated with the EF factor, $r = .24$, $p = .083$. Furthermore, significant correlations between all symptom domains were found, all rs > .30, all ps < .008.

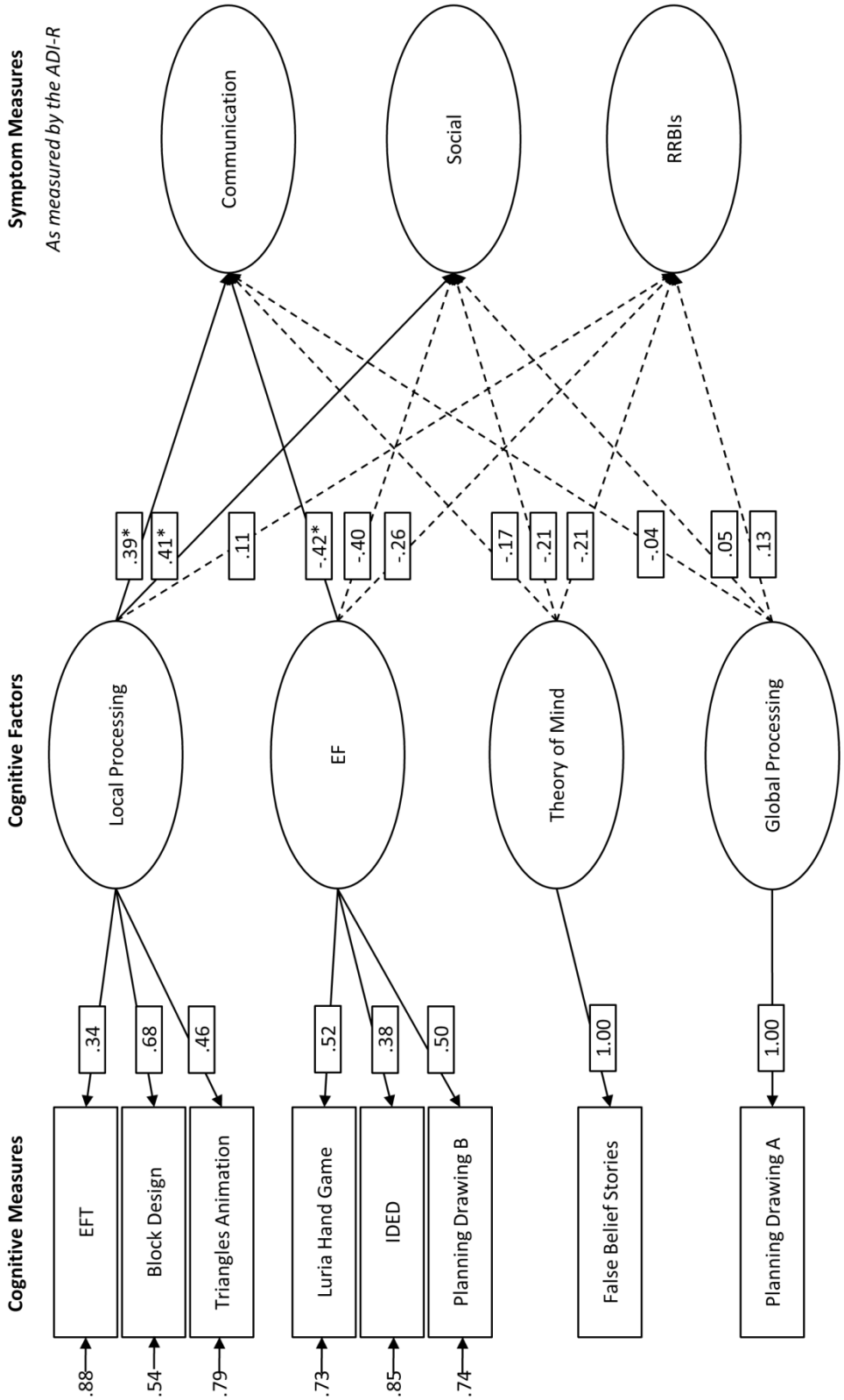
The relationship between cognitive and symptom domains was explored. EF was negatively related to ADOS communication and RRBI symptoms, and False-Belief Stories score was negatively related to ADOS social symptoms. All other relationships between cognitive domains and symptoms domains were not significant (all ps > .119). The model explained significant variation in all symptom domains; ADOS communication: $R^2 = .26$, $p = .024$; ADOS social: $R^2 = .22$, $p = .025$; ADOS RRBIs: $R^2 = .29$, $p = .042$.

Table 6.4. Path coefficients, standard error, and p-values for Structural Equation Models (SEMs) to investigate the relationship between cognitive domains and ASD symptoms.

	ADI SEM			ADOS SEM		
Structural model	*β*	S.E.	*p*-value	*β*	S.E.	*p*-value
Local processing → Communication	.39	.18	**.031**	.009	.21	.966
Local processing → Social	.41	.18	**.021**	-.02	.18	.937
Local processing → RRBIs	.11	.17	.512	.23	.20	.255
EF → Communication	-.42	.20	**.036**	-.46	.20	**.024**
EF → Social	-.40	.23	.084	-28	.18	.119
EF → RRBIs	-.26	.22	.246	-.55	.24	**.025**
False Belief → Communication	-.17	.14	.218	-.10	.13	.423
False Belief → Social	-.21	.15	.166	-.28	.13	**.024**
False Belief → RRBIs	-.21	.14	.142	-.07	.16	.647
Planning Drawing (coherence) → Communication	-.04	.11	.694	.005	.11	.965
Planning Drawing (coherence) → Social	.05	.11	.672	.09	.10	.358
Planning Drawing (coherence) → RRBI	.13	.10	.189	-.06	.11	.557

Abbreviations: ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; *β*= standardised coefficient; EF = executive function; S.E. = standard error, SEM = structural equation model

a) ADI-R Model


Symptom Measures
As measured by the ADI-R
Communication
Social
RRBIs
Cognitive Factors
Local Processing
EF
Theory of Mind
Global Processing
.39*
.41*
.11
-.42*
-.40
-.26
-.17
-.21
-.21
-.04
.05
.13
.34
.68
.46
.52
.38
.50
1.00
1.00
Cognitive Measures
EFT
Block Design
Triangles Animation
Luria Hand Game
IDED
Planning Drawing B
False Belief Stories
Planning Drawing A
.88
.54
.79
.73
.85
.74

b) ADOS Model

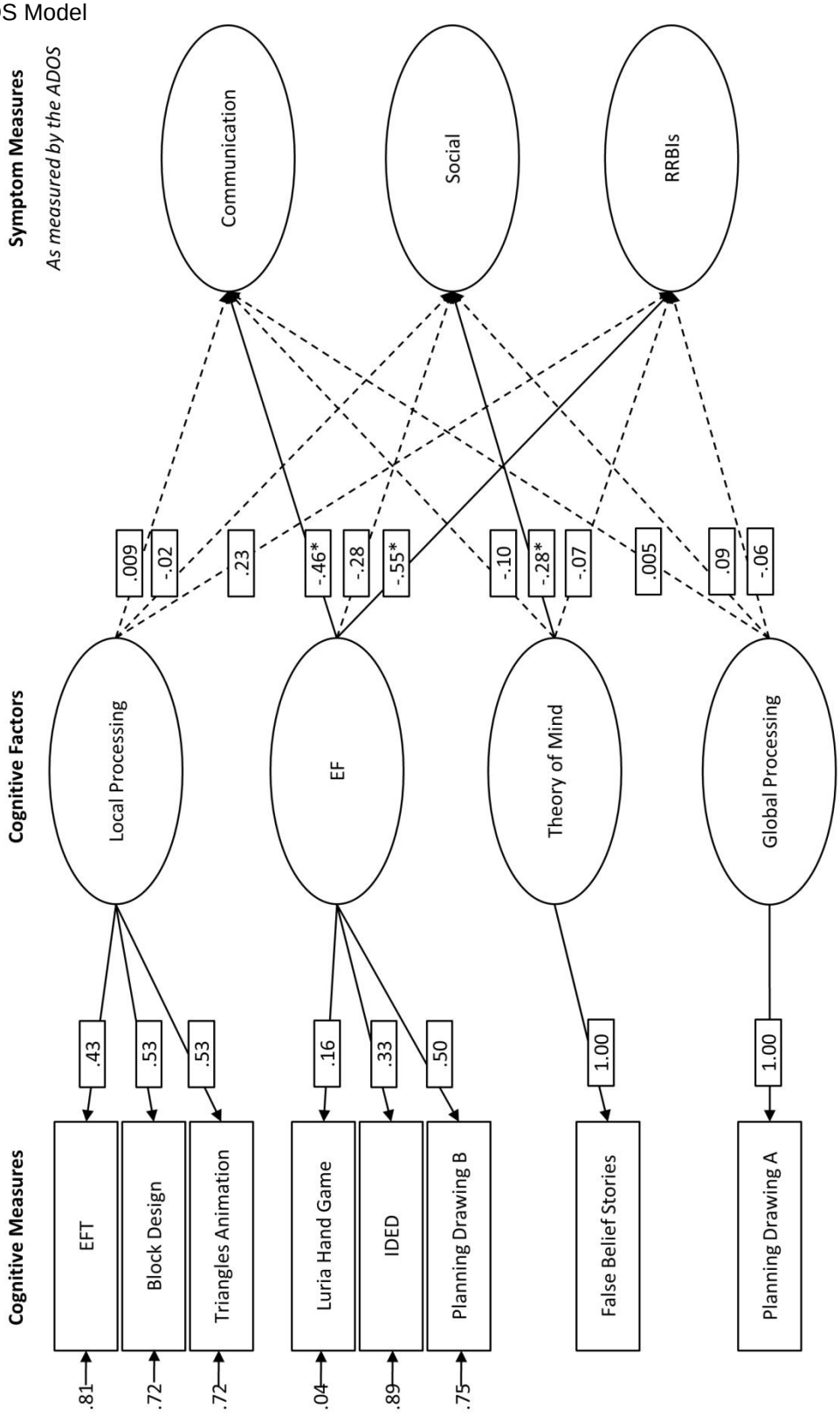


Figure 6.1. Results for the structural equation models to investigate the relationship between cognitive domains and symptoms using a) ADI-R and b) ADOS.

Note: Covariances between cognitive factors and between symptom measures are not displayed for clarity of diagram.

Higher scores for the cognitive measures and factors indicate better performance and higher scores for ADI and ADOS symptom domains indicate more severe symptoms. Dotted lines represent statistically non-significant paths. Circles represent latent variables. Squares represent observed variables. *$p < .05$.

Abbreviations: ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; EF = executive function; EFT = Embedded Figures Test; RRBIs = restricted and repetitive behaviours and interests

6.4 Discussion

The major aim of the current study was to investigate the relationship between performance on cognitive tasks and the symptoms domains of ASD. It was predicted that ToM performance would relate to social and communication symptoms and EF would relate to RRBIs. It was predicted that global processing would relate to communication symptoms and good local processing would not be impact on ASD symptoms. Using the ADOS as a measure of current symptom severity in ASD revealed that ToM was related to the social symptoms and EF was related to communication and RRBI symptoms of ASD. Using the ADI-R as a measure of past and current symptom severity in ASD, it was revealed that local processing was related to communication and social symptoms, and EF was related to communication symptoms in this ASD sample.

The findings partially support the predictions of the fractionated theory of ASD as the results from the ADOS model suggest that distinct cognitive features uniquely influence the current behavioural symptoms of ASD. However, the ADI model presents a different pattern of results that somewhat challenges the predictions of the fractionated theory of ASD, as distinct cognitive domains did not relate to specific behavioural symptoms. The disparate associations dependent on the diagnostic measure used may be due to differences in the way that symptoms are assessed in the ADI-R and ADOS. The ADOS is an observational assessment carried out by a trained researcher and measures current ASD behaviours. In contrast, the ADI-R is a parent-informant developmental history interview, which largely relies on retrospective data. It could therefore be considered that the ADI-R provides a lifespan perspective on ASD symptoms and so these findings may provide a suggestion of a longitudinal relationship between cognition and behavioural domains. It is also possible that parents' memory of early symptoms is coloured by

current difficulties or changes in functioning. Using both diagnostic measures obtains more comprehensive information on the individuals' symptomatology and so may provide a more valid representation of the individual's symptom profile.

The hypothesis that was tested in this study and the one suggested by the fractionable triad postulates a *direct* effect between cognition and behaviour. In relation to the current findings for example, aspects of EF may be needed for effective communication, such as *inhibition* of inappropriate dialogue, keeping what the other speaker has said in *working memory*, *flexibility* in providing a response, *attention* to communicative cues, and *initiation* of communicative behaviour. Furthermore, deficits in EF may contribute to RRBIs through difficulties in *inhibiting* inappropriate behaviour, *shifting* between behaviours, and *generating* appropriate new behaviours. Local-processing or good attention to details may alleviate social and communication symptoms as individuals may be able to use this skill to help in social interactions and for social communication. In addition, an impaired ability to represent mental states (ToM) could limit social interactions. However, the fractionable triad account does not consider *indirect* effects in the link between a cognitive domain and a symptom domain, such as the role of mediating factors, a combination of factors, such as multiple cognitive domains together, or *bidirectional* effects between cognition and behaviour, which could also be important.

Considering the current results in relation to past findings, a link between EF and communication has not been widely reported (e.g., Joseph & Tager-Flusberg, 2004). However, Pellicano (2013) found that EF was related to both social-communication symptoms and RRBIs, with the conclusion that EF has a more extensive role in influencing the behavioural symptoms of ASD than has been considered. Aspects of EF, such as difficulties in inhibiting inappropriate behaviour, shifting set, and generating appropriate new behaviours, have been hypothesised to underlie RRBIs (Turner, 1997). In addition, empirical evidence that inhibition of prepotent responses (Mosconi, et al., 2009), generativity (Turner, 1995), set-shifting (Yerys, et al., 2009), and cognitive flexibility (South, et al., 2007) relate to RRBIs in ASD has been reported, in line with the present finding of a link between EF and RRBIs as measured by the ADOS. In addition, previous findings favour a link between ToM and social skills in ASD in line with the present finding that poorer false-belief understanding was predictive of more severe social-interaction symptoms on ADOS.

Regarding local/global processing, previous studies have not reported an association between local processing and symptom domains (Loth, et al., 2010; Teunisse, et al., 2001; White & Saldana, 2011). By contrast, our data suggested that better performance on local processing tasks was associated with fewer social and communication symptoms on ADOS. This may indicate that increased local processing ability may be a compensatory skill in ASD that could alleviate some symptom impairments. Our factor analysis suggested separate factors for local and global processing, and performance on the latter did not relate to any symptom domains in our study. This finding fits with those reported by Pellicano (2013), but stand in contrast to predictions that integrative, contextual processing is necessary for social adaptation or communication (Noens & van Berckelaer-Onnes, 2004; Noens & van Berckelaer-Onnes, 2005). Our findings may indicate that aspects of processing style described by 'weak coherence' are not relevant to diagnostic symptoms of ASD, or that their impact is on aspects of behaviour not measured here (e.g., uneven cognitive profile, talents, narrow interests). For example, Vital, Ronald, Wallace, and Happé (2009) found that special abilities were more strongly associated with RRBIs (specifically an eye for detail) than with social or communication symptoms, in TEDS.

The findings of this study are somewhat problematic for the predictions of the fractionable triad. On the one hand, distinct cognitive functions were found to underlie the symptom domains of ASD when measured using the ADOS. However, the ADI model presents a different pattern of results that somewhat challenges the predictions of the fractionated theory of ASD. In addition, there were significant correlations between cognitive factors and also between symptom domains. These findings do not appear to fit a strong form of the fractionated triad account – although it should be noted that the present sample comprised only diagnosed ASD individuals, who are selected to show all three parts of the triad; different findings might emerge in a population sample unselected for the ASD symptom triad. In contrast to a strong 'fractionated' account, the multiple cognitive deficit model of ASD would instead predict inter-relation amongst cognitive functions due to overlapping developmental pathways and interactive processes (Pennington, 2006). Additionally, this model proposes that it is this interaction between multiple cognitive deficits in ASD that influences symptom severity. There are also likely to be multiple pathways from cognition to symptoms due to the heterogeneity inherent in ASD. The current results do strongly suggest the need to move away from single deficit models of ASD, which

have recently become popular again with the implication that ASD is caused by a failure of Bayesian inference (e.g., Pellicano & Burr, 2012). However, there are challenges to overcome in the move to multiple deficit models of ASD, such as how to test these models. Overall, it seems that multiple cognitive deficits are characteristic of ASD, and these influence symptom severity.

6.4.1 Limitations

Limitations of the current study should be taken into account when considering the results. Firstly, the cognitive tasks were used to predict ASD symptomatology but there is no experimental evidence of direction of causation: the severity of symptoms could impact the development or manifestation of cognitive abilities. Secondly, the cognitive measures may not have fully encapsulated the cognitive ability that they were purported to measure. For example, ToM was based solely on false-belief understanding. Finally, there were some inherent issues within the sample used in the current study. Although the SR study sample was population-based, the sample was not chosen at random and so may be subject to sampling bias. There were power issues in the current study; for example, it was not possible to conduct SEM models using the unaffected co-twins due to the sample size being too small. However, the current study has some advantages over previous studies in that it is based on a large population-based study, with an ASD group that covered the whole ASD spectrum. The study also included a measure of IQ to ensure that the effect of IQ could be accounted for in the results.

6.4.2 Conclusion

The results were dependent on which diagnostic measure was used. Using the ADOS as a measure of current ASD symptomatology indicated that ToM was associated with social symptoms in ASD and EF was associated with communication symptoms and RRBIs in ASD. Using the ADI as a parent-reported measure of past and present ASD symptomatology indicated that local processing was associated with social and communication symptoms, and EF was associated with communication symptoms of ASD. It may be useful to explore the cognitive features of ASD symptomatology at different ages in development as links between cognitive features of ASD and symptoms may alter throughout development. The findings suggest the need to move away from single cognitive deficit accounts of ASD and consider that multiple cognitive deficits could underlie the symptoms of ASD.

The results of this study suggest that specific cognitive atypicalities are related to specific ASD symptoms. Therefore, it would be valuable to investigate the magnitude of genetic associations between these cognitive atypicalities and specific ASD symptoms. However, it is not possible in the scope of this thesis due to the nature of the selected sample, as the ASD symptoms could not be estimated separately within a twin model. However, the next chapter investigates the genetic overlap between cognitive atypicalities and ASD as a whole.

Chapter 7 Genetic and Environmental Overlap Between Cognitive Atypicalities and Autism Spectrum Disorder

It was shown in Chapter 4 that cognitive atypicalities in central coherence, executive function and theory of mind are highly prevalent in ASD, with nearly a third of those with ASD exhibiting multiple cognitive atypicalities. These cognitive atypicalities across the three main cognitive domains could potentially be cognitive endophenotypes of ASD. Chapter 6 indicated that these cognitive atypicalities underlie certain ASD symptoms. However, there have been few twin studies into the heritability of these cognitive atypicalities, with no studies conducted in the ASD population. The aim of Chapter 7 is therefore to examine the heritability of these cognitive atypicalities and the genetic and environmental overlap between cognitive atypicalities and ASD using the twin sample in the Social Relationships (SR) study.

7.1 Introduction

Autism spectrum disorder is a highly heritable neurodevelopmental disorder characterised by social-interaction and social-communication impairments and restricted and repetitive behaviours and interests (RRBIs). Previous twin studies have provided compelling evidence that ASD has a large genetic component, typically demonstrating high heritability estimates (60-90%) and indicating low contributions of the shared environment. In addition, previous analyses using the sample from the Social Relationship (SR) study have also estimated the heritability of ASD to be between 56-95%, dependent on the diagnostic assessment used (Colvert, et al., 2015). Underlying the symptoms of ASD are postulated cognitive atypicalities in the domains of central coherence, executive function and theory of mind. However, there have been no studies to quantify the extent to which liability to ASD overlaps genetically with these cognitive atypicalities. This chapter sought to examine the genetic and environmental contributions to the variance of these cognitive domains and their covariance with ASD.

Cognitive atypicalities appear to be highly prevalent in ASD. Atypical performance across tasks assessing the three cognitive domains of central coherence, executive function, and theory of mind has been reported in ASD twins (Chapter 4). In ASD, 19% of adolescents had a cognitive atypicality (defined as performing 1 SD below the SR study sample of typically-developing controls) in at least one cognitive domain, 40% had co-occurring cognitive atypicalities, and

32% had multiple cognitive atypicalities (Chapter 4). The issue of whether these cognitive atypicalities are heritable and share common influences with ASD is important for informing theories of ASD. These cognitive atypicalities may be viable cognitive endophenotypes of ASD if they are heritable and in addition show evidence of shared genetic influences with ASD (Doyle et al., 2005). To date, no such studies have been conducted in a clinically ascertained ASD twin sample.

7.1.1 Twin Studies in Typical Development

There have been a handful of twin studies within the typically-developing population investigating the heritability of cognitive domains associated with ASD.

7.1.1.1 Executive Function

Twin studies into the aetiology of executive functions have found moderate genetic (40-60%), no shared environment, and moderate non-shared environmental influences on cognitive task performance measuring different aspects of executive function (e.g., Ando, Ono, & Wright, 2001; Malone & Iacono, 2002; Wright et al., 2001). The sample size in these studies ranged from small (143 MZ and 93 DZ pairs, Ando et al., 2001) to large (900 MZ and 800 DZ pairs, Wright et al., 2001). One twin study with a sample of 316 MZ and 266 DZ twin pairs found that individual differences in executive function were almost entirely genetic, with a highly heritable common executive function factor (99%) made up of inhibition, shifting, and updating (Friedman et al., 2008).

7.1.1.2 Theory of Mind

The first twin study in the aetiology of theory of mind found that performance in 61 MZ and 58 DZ 3-year-old twin pairs was 67% heritable (95% confidence interval; CI: 26-79%), with no influence of the shared environment, and moderate influence of the non-shared environment (32%; CI: 21-49%), which were independent of verbal IQ (Hughes & Cutting, 1999). In contrast, Hughes et al. (2005) found that environmental factors (both shared and non-shared) explained the majority of the variance in theory of mind performance in 312 MZ and 246 DZ 5-year-old twin pairs. The difference in results between the two studies was largely concluded to be due to insufficient power in the earlier study, but could also point to a longitudinal model in which individual differences in early theory of mind development are largely influenced by genes and later theory of mind ability is influenced by environmental effects. A third study with a much

larger sample of approximately 4000 twin pairs found results that fell in-between these two studies, with theory of mind performance between the ages of 2 and 4 showing modest genetic influences (25-57%), low to modest shared environmental influences (17-43%) and modest non-shared environmental influences (24-46%) (Ronald, Happé, Hughes, & Plomin, 2005).

Reviewing the limited twin studies into the heritability of the cognitive domains associated with ASD, executive function appears to be largely genetic, with age-dependent results for the heritability of theory of mind. There are no twin studies exploring the concept of central coherence in typical development.

7.1.2 Twin Studies in Clinical Populations

There have also been limited twin studies into the heritability of some of these cognitive domains and their (genetic) association with clinical disorders.

7.1.2.1 Executive Function

Coolidge, Thede, and Young (2000) investigated the heritability and comorbidity of ADHD with behavioural disorders and executive function deficits. Executive function deficits were largely due to genetic factors (.77) with no evidence for shared environmental influences. There was also a substantial genetic overlap between ADHD and executive function deficits (phenotypic correlation = .83; genetic correlation = .79). In schizophrenia, common genetic factors accounted for a large portion of the variance between schizophrenia and executive function test performance (Owens et al., 2011). In bipolar disorder, the additive heritability of executive functions was estimated to be between 52-60% (Antila et al., 2007).

7.1.2.2 Central Coherence

For eating disorders, central coherence has suggested to have a genetic basis, with an environmental basis suggested for set-shifting (an aspect of executive function) (Kanakam, Raoult, Collier, & Treasure, 2013).

7.1.3 Family Studies in ASD Populations

Even though there have been limited twin studies, the genetic liability for specific cognitive deficits has been investigated in family studies of the broader autism phenotype (BAP). Happé, et al. (2001) found that fathers of boys with ASD showed enhanced local processing, indicating that local processing may be part of the BAP. Nyden, Hagberg, Gousse, and Rastam (2011)

investigated central coherence, executive function, theory of mind, and intellectual ability as intermediate cognitive phenotypes of ASD using ASD probands and their affected and unaffected relatives. Findings suggested that weak central coherence and theory of mind deficits were not part of the broader autism phenotype. However, all family members showed affected planning ability, but preserved set-shifting. This finding suggests that executive functions characterise the broader autism phenotype. However, Losh et al. (2009) found that only theory of mind, not executive function or central coherence, was part of the BAP. In addition, Sucksmith, et al. (2011) reviewed the existing research findings and found that the broader autism phenotype was characterised by cognitive deficits (including theory of mind deficits, deficits in executive function, and local processing).

7.1.3.1 Present Study

To date, no study in a clinically ascertained ASD twin sample has investigated the genetic and environmental contributions to the variance of cognitive domains (central coherence, executive function or theory of mind) and their covariance with ASD. It was predicted that the cognitive atypicalities would be moderately genetic based on previous twin and family studies. It has been shown previously that cognitive atypicalities are a core characteristic of ASD (Chapter 4). The aim of the current study was to investigate to what extent these cognitive atypicalities are heritable and to what extent the association with ASD is genetically or environmentally driven. No specific predictions were made but showing significant heritability as well as genetic overlap would allow identifying the cognitive atypicalities that are most likely valid cognitive endophenotypes of ASD.

The present study applied a bivariate twin model fitting approach on data from a population sample of adolescent twins with and without a diagnosis of ASD, as well as a control sample of twins, to investigate how much of the phenotypic association between cognitive domains and ASD is due to genetic and environmental factors. Furthermore, the relative contribution of genetic and environmental effects to individual differences in cognitive performance in central coherence, executive function and theory of mind was estimated.

7.2 Method

7.2.1 Sample and Procedure

Participants were part of the Twins Early Development Study (TEDS), a population-based longitudinal study of all twins born in the UK between 1994 and 1996. The 12,054 families involved at the start of TEDS were reported to be representative of UK families (Haworth, et al., 2013). Zygosity was assessed using a standard zygosity questionnaire (Goldsmith, 1991), which proved to be accurate in 95% of the cases (Price et al., 2000). For the remaining pairs, zygosity was assessed on the basis of full DNA tests.

The analyses presented in this chapter used the SR study sample, as described in Chapter 3. The SR study focused on those TEDS families with one or both twins meeting diagnostic criteria for ASD. Participants were diagnosed with ASD using gold-standard diagnostic instruments; the ADI-R (Lord, et al., 1994) and the ADOS (Lord, et al., 2000). Additional cut-offs devised by the Autism Genetic Resource Exchange (AGRE) were implemented to identify individuals with more subtle ASD symptoms and assigned cases to 'ASD' (AGRE categories Autism and 'Not Quite Autism'), 'Broad Spectrum Disorder', and 'unaffected'. The ASD group consisted of 27 monozygotic (MZ) and 100 dizygotic (DZ) twin pairs. The control group consisted of 28 MZ and 52 DZ twin pairs. Table 7.1 shows the number of twin pairs who were concordant and discordant for a diagnosis of broad spectrum and ASD (combined) in the SR study. Mean age of the ASD twin pairs was 13.50 years (SD = 0.68) and the control twin pairs was 12.79 years (SD = 1.10).

Table 7.1. Number of twin pairs within the SR study

	ASD concordant	ASD discordant	Controls
MZ twin pairs (55)	24	3	28
DZ twin pairs (152)	30	70	52
Total twin pairs (207)	54	73	80

Home visits were made to all ASD and control families by two trained researchers. The ASD families completed two home visits, which lasted approximately six hours in total. The ASD families completed gold standard diagnostic assessments; the ADOS (Lord, et al., 2000) and

the ADI-R (Lord, et al., 1994). The control families completed one home visit, which lasted approximately two hours. Both the ASD and control families completed an extensive cognitive battery (see Chapter 3). The batteries were administered in a counterbalanced order with two fixed orders of tasks. A different experimenter assessed each participant within the twin pair in order to reduce possible experimenter bias.

7.2.2 Measures

7.2.2.1 Intellectual Ability

Intellectual ability was assessed using the WASI (Wechsler, 1999) to obtain an estimated score for IQ. The current study used the Block Design subtest as a measure of CC. Therefore, the two-subtest version of the WASI (Matrix Reasoning and Vocabulary) was used to estimate full-scale IQ.

7.2.2.2 Cognitive Factors

The cognitive task battery is described in Chapter 3. Briefly, the cognitive task battery contained twelve cognitive tasks and was designed to assess ability across cognitive domains, including central coherence, executive function, and theory of mind.

Four cognitive factors were created based on exploratory factor analysis (EFA) and confirmatory factor analysis carried out in Chapter 5 using cognitive task performance in the battery (see Table 7.2). A factor score was saved for each participant in relation to each identified factor. Four separate factor scores were calculated by multiplying the factor loading (from EFA; Table 5.2) by the item score for each item identified to be relevant to each factor before summing to gain unit-weighted factors.

Table 7.2. Cognitive tasks comprising cognitive factors

Cognitive Factor	Cognitive Tasks
Local Processing Factor	EFT, Block Design Task, Triangles Animation Task
Executive Functioning Factor	Luria Hand Game, ID/ED, Planning Drawing Task, Part B (planning score)
Theory of Mind	False-Belief Stories
Global Processing Factor	Planning Drawing Task, Part A (coherence score)

7.2.2.3 Best Estimate Consensus Diagnosis (CD)

Best-estimate diagnoses were assigned, blind to zygosity and co-twin diagnostic status, following review of all available information (ADI-R, ADOS, DAWBA, clinical reports). When all available sources of information were in agreement, cases were assigned to that category. In 89 cases the diagnostic classifications across instruments were inconsistent. In these cases all available data were assessed by clinical experts and consensus best-estimate diagnoses were assigned on the basis of this review. A Consensus Diagnosis (CD) was used in analyses as a three-category measure of ASD: 0 = no ASD/controls, 1 = Broad Spectrum, 2 = ASD.

7.2.3 Analyses

7.2.3.1 Preparation of Data Prior to Model Fitting

Prior to model fitting, the effects of age, sex, and IQ were regressed out of the performance in the cognitive factors to account for sources of variation in performance in cognitive variables (a standard twin model procedure to prevent over-inflation of C-estimates; McGue & Bouchard, 1984). The residuals were then normalised using a log-transformation. ASD status (consensus diagnosis; CD) was used as an ordinal variable (0 = no ASD/control, 1 = Broad Spectrum, 2 = ASD).

7.2.3.2 Background to Twin Model-Fitting

Univariate genetic models partition twin-pair correlations into genetic and environmental effects by comparing MZ twins and DZ twins on a particular trait as MZ twins share 100% of their genes compared to 50% for DZ twins. The phenotypic variance of measures can be partitioned into genetic (A), shared environment (C) and non-shared environment (E) effects. Any possible measurement error is also included in E. If the phenotypic similarity of MZ twin pairs is more than twice that of DZ twin pairs, then it suggests the presence of A for the trait. If the phenotypic similarity of DZ twin pairs is greater than half the MZ twin correlation, then it suggests the presence of C for the trait. The extent to which MZ twins are different from each other reflects E (Rijsdijk & Sham, 2002).

7.2.3.3 Twin Correlations

Using full information maximum likelihood estimation, continuous (cognitive factor scores) and ordinal measures (CD) were analysed jointly assuming a liability threshold model for ASD. To

correct for ascertainment, ASD thresholds were fixed to known population prevalence: Broad Spectrum; 5% = 1.94, ASD; 1% = 2.33 (z-values). The joint continuous-ordinal liability threshold model estimates the MZ and DZ twin correlations both within and across ASD and cognitive factor scores. The constrained model estimates the phenotypic correlation between the variables (e.g., executive function with liability to ASD), regardless of zygosity or birth order. This model also calculates twin correlations for each variable individually (cross-twin within-trait), as well as one set of cross-twin cross-trait correlations for MZ and DZ pairs. Significant cross-twin within-trait covariances suggest aetiological influences for ASD and cognitive factors. Significant cross-twin, cross-trait covariances suggest that these common aetiological influences between ASD and the cognitive factor score are familial (Rijsdijk & Sham, 2002). If the MZ/DZ ratio of the cross-trait cross-twin correlations is 2:1, it further suggests that the overlap is due to genetic influences; whereas a ratio of 1:1 suggests that the overlap is due to shared environmental influences. Non-significant cross-twin cross-trait correlations would suggest that the shared aetiological influences between ASD and the cognitive factors are due to non-shared environmental influences.

7.2.3.4 Bivariate Twin Model

Bivariate genetic model-fitting analysis was performed to estimate the heritability of cognitive factors as well as the genetic and environmental overlap (covariance) between ASD and cognitive factors in the current sample of twin pairs. The bivariate model was fitted separately for each cognitive factor score and ASD combination.

A Cholesky decomposition was fitted to the data (Figure 7.1). A Cholesky decomposition uses a triangular decomposition to assess the extent to which the genetic and environmental factors covary, and is preferred for optimisation reasons. However, since the Cholesky decomposition gives precedence to the first selected variable, the correlated factor solution (Loehlin, 1996) was interpreted so that the order of traits is arbitrary. Figure 7.2 shows the correlated factors model with estimates of genetic (r_A), shared environmental (r_C) and non-shared environmental correlations (r_E) between the variables. These correlations are estimated between 0 (no overlap between factors influencing traits) and 1 (complete overlap in factors influencing the traits). For example, a genetic correlation (r_A) of 1 would indicate that the same genetic factors influence

both ASD and the cognitive factor, whereas a correlation of 0 would indicate that ASD and the cognitive factor are influenced by independent genetic factors.

7.2.3.5 Structural Equation Model Fitting

The (genetic) models were fitted in the structural equation modelling program OpenMx (Boker et al., 2011). This program is designed to interpret predictions of the variances and covariances of the variables using specified parameters and matrix algebra. These predictions are linked back to the observations of the real data in order to estimate the most likely values of the free parameters (see Appendix 3 for annotated script for current analyses). Maximum-likelihood estimation was used on raw data, accounting for missing-ness of observations. Estimates are provided with 95% confidence intervals (the inclusion of zero indicating non-significance). Model fit is indicated by minus twice the log-likelihood of the data (-2LL), which is a relative measure of fit, meaning that the difference in -2LL of nested models is distributed as Chi-square with Degrees of Freedom (DF) equivalent to the difference in DF of the nested models. Model comparison for non-nested models are made using Akaike's Information Criterion (AIC), a goodness-of-fit index that penalises models for increasing complexity and accounts for sample size, with increasingly negative values corresponding to increasingly better fitting models. There are no statistical tests to compare two AIC values, but guidelines suggest that a difference of 3-7 can be considered good support for model selection (Burnham & Anderson, 2002).

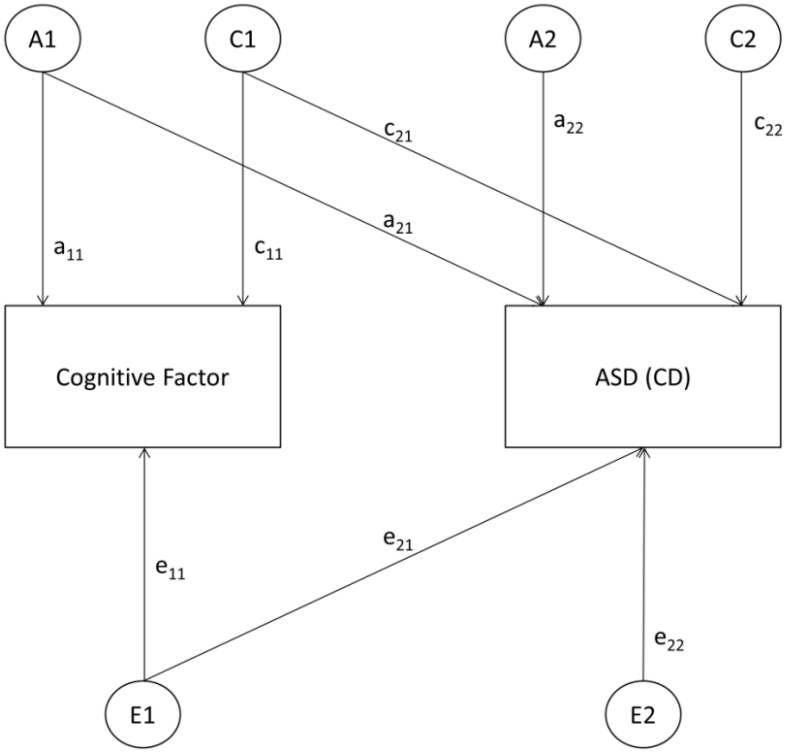


Figure 7.1. Path diagram for the bivariate ACE twin model: Cholesky decomposition.

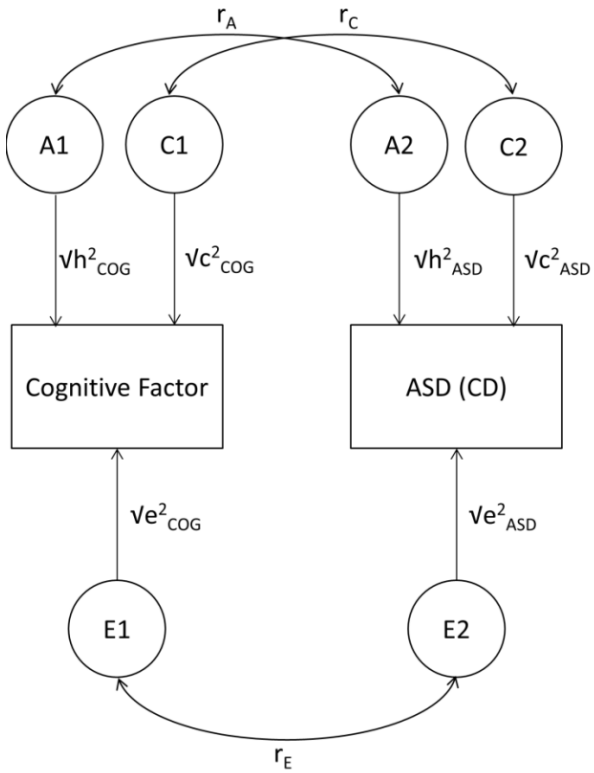


Figure 7.2. Path diagram for the bivariate ACE twin model: Correlated factors solution.

7.3 Results

Means and standard deviations of participant characteristics and cognitive factors are given in Table 7.3.

Table 7.3. Participant characteristics with IQ-adjusted cognitive factors

	ASD Concordant		ASD Discordant		Controls	
	MZ	DZ	MZ	DZ	MZ	DZ
	(*N* = 48)	(*N* = 60)	(*N* = 6)	(*N* = 140)	(*N* = 56)	(*N* = 104)
Age	13.61	13.39	13.58	13.50	12.83	12.77
	(0.82)	(0.64)	(0.13)	(0.66)	(1.26)	(1.01)
IQ	88.46	94.26	82.67	96.74	104.13	100.71
	(18.06)	(19.12)	(23.35)	(20.08)	(13.45)	(15.92)
Local Processing	-0.55	-0.49	-0.55	-0.52	-0.52	-0.52
Factor	(0.14)	(0.16)	(0.14)	(0.13)	(0.12)	(0.13)
EF Factor	-0.53	-0.43	-0.57	-0.45	-0.35	-0.33
	(0.25)	(0.21)	(0.19)	(0.19)	(0.12)	(0.16)
ToM Factor	-0.37	-0.33	-0.37	-0.32	-0.30	-0.28
	(0.26)	(0.22)	(0.28)	(0.19)	(0.15)	(0.15)
Global Processing	-0.46	-0.39	-0.42	-0.41	-0.39	-0.38
Factor	(0.20)	(0.21)	(0.23)	(0.20)	(0.16)	(0.18)

7.3.1 Phenotypic Correlations

Model fitting estimates of the phenotypic correlations between cognitive factors and ASD (CD) are presented in the Table 7.4. Three of the cognitive factors showed modest correlations with ASD (CD). The local processing factor did not show a significant association with ASD (CD).

Table 7.4. Phenotypic correlations between cognitive factors and ASD (CD)

Cognitive Factor	Phenotypic Correlations r_{ph} with ASD (95% CI)
Local Processing	-.03 (-.06/.13)
Executive Functioning	**-.25*** (-.33/-.17)
Theory of Mind	**-.16*** (-.24/-.07)
Global Processing	**-.12*** (-.20/-.04)

Note: 95% confidence intervals in parentheses

*significant estimates (the 95% CIs excluding 0 indicate statistical significance)

7.3.2 Twin Correlations

Cross-twin within-trait correlations for ASD (CD) and cognitive factors as well as the cross-twin cross-trait correlations for cognitive factors and ASD (CD) are reported in Table 7.5. The DZ cross-twin within-trait correlations were less than half that of the MZ correlations for the local and global processing factors, indicating genetic influence for central coherence in the present sample. However, the cross-twin within-trait MZ correlation for global processing was non-significant. The DZ correlation was higher than the MZ correlations for the executive function and theory of mind factors, indicating a large role for the non-shared environment.

None of the cognitive factors that had a significant phenotypic correlation with ASD showed heritable influences, and therefore are unlikely to be potential cognitive endophenotypes. This will be further tested in the genetic models. The twin correlations for both global processing and ToM suggest that they are not possible endophenotypes for ASD and that the significant correlation with ASD is mostly determined by non-shared environmental effects. The correlations for EF are not easy to interpret, but there are most likely effects of shared and non-shared environment.

Table 7.5. Cross-twin within-trait and cross-twin cross-trait correlations for cognitive factors and ASD (CD)

Cognitive Factor	Cross-Twin Within-Trait Correlations *r* (95% CI)		Cross-twin Cross-Trait Correlations *r* (95% CI)	
	MZ	DZ	MZ	DZ
Local Processing	**.68*** (.50/.79)	**.23*** (.04/.39)	**.12*** (.01/.23)	.00 (-.10/.10)
EF	.09 (-.22/.38)	**.21*** (.03/.37)	**-.24*** (-.12/-.36)	**-.13*** (-.22/-.03)
Theory of Mind	.03 (-.20/.25)	.05 (-.14/.24)	-.08 (-.19/.03)	-.03 (-.12/.07)
Global Processing	.31 (.00/.54)	-.02 (-.18/.14)	-.12 (-.23/-.00)	.04 (-.13/.04)

Note: Cross-twin, within-trait correlations for consensus diagnosis for ASD across all cognitive factors were: *r*MZ = .91-.92, *r*DZ = .46-.47. 95% confidence intervals in parentheses. *significant estimates (95% CIs excluding 0 indicate statistical significance)

7.3.3 Bivariate Genetic Model-Fitting Results

To investigate how much of the phenotypic correlation between the cognitive factors and ASD (CD) is due to shared genetic or environmental factors, a series of bivariate genetic model-fitting analyses were carried out, separately for each cognitive factor. In each, ACE model estimates of the genetic and environmental influences (A = genetic effects; C = shared environment, E = non-shared environment) on the cognitive factor, as well as the genetic (r_G) and environmental (r_E) correlations between the cognitive factor and ASD (CD) were obtained. Table 7.6 provides the fit statistics of these models, including those of the correlation models.

Table 7.6. Fit statistics

Cognitive Factor Model	Model	ep	-2LL	df	AIC
Local Processing	1. Cor	9	929.07	750	-570.93
	2. BivACE	9	932.37	750	-567.63
Executive Functioning	1. Cor	9	1170.00	745	-320.00
	2. BivACE	9	1170.65	745	-319.35
Theory of Mind	1. Cor	9	1149.73	761	-372.27
	2. BivACE	9	1149.77	761	-372.23
Global Processing	1. ConSat	9	1157.48	790	-422.52
	2. BivACE	9	1162.91	790	-417.09

Abbreviations: -2LL = likelihood of the data; AIC = Akaike's Information Criteria; BivACE = bivariate genetic model; Cor = correlation model; df = degrees of freedom; ep = estimated parameters

Table 7.7 shows parameter estimates for the ACE model for each cognitive factor, indicating the proportion of variation explained by genetic effects (h^2), shared environmental effects (c^2), and non-shared environmental effects (e^2). ASD (CD) showed strong genetic effects (.82-.89), low shared environmental effects (.03-.08) and weak non-shared environmental effects (.08-.10). The local processing factor showed strong genetic influence (.61). All other cognitive factors showed low genetic influence (.01-.06). The local processing factor showed moderate non-shared environmental influence (.36). All other cognitive factors showed substantial non-shared environmental influence (.80-.95). All cognitive factors showed low, non-significant shared environmental influence (.03-.15).

Table 7.7. Genetic, shared, and non-shared environmental estimates of the full ACE genetic model for each cognitive factor

Cognitive Factor Model	Cognitive Factor		
	h^2 (95% CI)	c^2 (95% CI)	e^2 (95% CI)
Local Processing	**.61*** (.26/.77)	.03 (.00/.42)	**.36*** (.23/.56)
Executive Functioning	.05 (.00/.21)	.15 (.00/.32)	**.80*** (.65/.95)
Theory of Mind	.01 (.00/.24)	.04 (.00/.18)	**.95*** (.81/.99)
Global Processing	.06 (.00/.34)	.06 (.00/.18)	**.88*** (.65/.99)

Note: 95% confidence intervals in parentheses. Significance is indicated by confidence intervals that exclude zero.

Abbreviations: c^2 = shared environment estimate; CI = confidence intervals; e^2 = non-shared environment estimate; h^2 =genetic estimate

Table 7.8 shows the contribution of genetic ($r_{ph\text{-}A}$) and shared ($r_{ph\text{-}C}$) and non-shared environmental ($r_{ph\text{-}E}$) factors to the phenotypic correlations ($r_{ph\text{-}E}$) between cognitive factors and ASD (CD), as well as the genetic (r_A) and shared (r_C) and non-shared (r_E) environmental correlations between cognitive factors and ASD (CD). These results are also presented as path diagrams in Figure 7.3. All genetic correlations were non-significant. Local processing showed a modest (non-significant) genetic correlation with ASD, and a moderate (non-significant) environmental correlation with ASD. Most of the phenotypic correlation between ASD and executive functioning was explained by (non-significant) shared genetic effects. Theory of mind showed a modest (non-significant) environmental correlation with ASD. Results indicated that half of the phenotypic correlation between ASD and theory of mind was explained by overlapping non-shared environmental effects. Global processing showed a (non-significant) strong genetic correlation with ASD. Results also indicated that most of the phenotypic correlation between ASD and global processing was explained by shared genetic effects.

Table 7.8. Phenotypic correlations between cognitive factors and ASD (CD) and the contribution of genetic and environmental factors as predicted by the full ACE models and A, C, and E correlation estimates

Cognitive Factor	$r_{ph\text{-}A}$	$r_{ph\text{-}C}$	$r_{ph\text{-}E}$	r_{ph}	r_A	r_C	r_E
Local Processing	.15	-.02	-.07	.04	.21	-.99	-.43
	(-.06/.12)	(-.21/.01)	(-.17/.00)	(-.08/.14)	(-.05/.27)	(-.99/.99)	(-.60/.06)
Executive	-.21	-.02	-.02	**-.25***	-.99	-.36	-.07
Functioning	(-.39/.00)	(-.11/.17)	(-.07/.11)	(-.34/-.17)	(-.99/.99)	(-.99/.99)	(-.66/.26)
Theory of Mind	-.10	.02	-.08	**-.16***	-.99	.99	-.27
	(-.23/.04)	(-.11/.10)	(-.23/.00)	(-.24/-.08)	(-.99/.99)	(-1.00/.99)	(-.60/.03)
Global	-.15	.07	-.05	**-.12***	-.67	.99	-.16
Processing	(-.47/.02)	(-.09/.14)	(-.15/.05)	(-.21/-.04)	(-.90/.57)	(-.87/.99)	(-.47/.19)

Note: 95% confidence intervals in parentheses. Significance is indicated by confidence intervals that exclude zero.

Abbreviations: r_A = genetic correlation; r_C = shared environment correlation; r_E = non-shared environment correlation; r_{ph} = phenotypic correlation; $r_{ph\text{-}a}$ = phenotypic correlation due to genetic effects; $r_{ph\text{-}c}$ = phenotypic correlation due to shared environment; $r_{ph\text{-}e}$ = phenotypic correlation due to non-shared environment

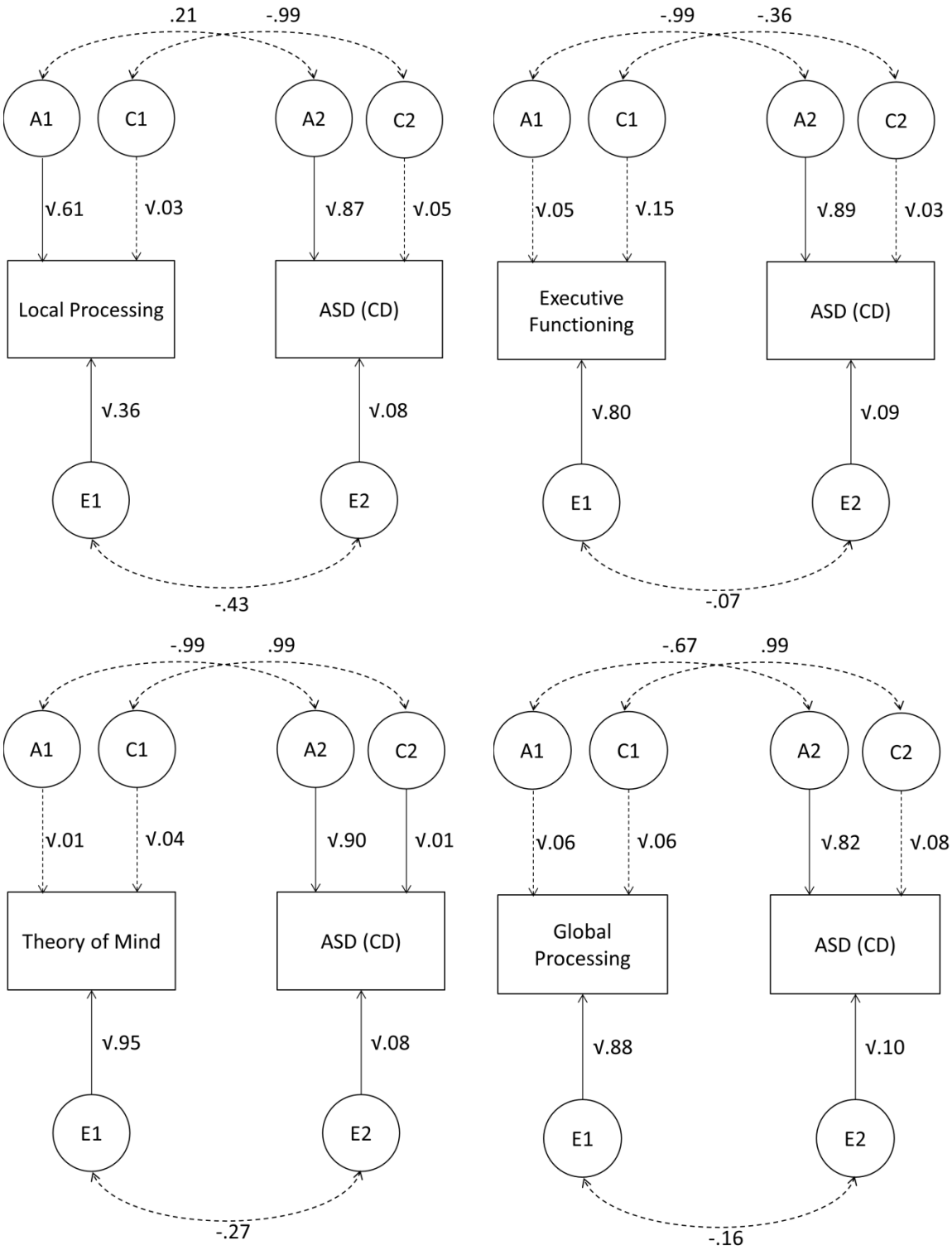


Figure 7.3. Path diagrams indicating the results from the bivariate ACE models for ASD and each cognitive factor.

Notes: Rectangular boxes indicate observed variables, circles indicate latent factors (A, C, E), double-headed arrows indicate correlations, single-headed arrows indicate causal pathways, dotted lines represent non-significance

7.4 Discussion

7.4.1 Summary of Findings

The current chapter examined the genetic and environmental contributions to variance in the cognitive domains of central coherence, executive function and theory of mind, and their covariance with ASD. This is the first twin study to examine the heritability of the cognitive domains of central coherence, executive function and theory of mind in adolescence, and the genetic and environmental correlations between these cognitive domains and ASD.

There were significant associations between cognitive domains and ASD, with poorer global processing, executive function and theory of mind being related to an increased liability to ASD. Local processing was not associated with ASD. Executive function showed the highest phenotypic correlation with ASD.

Findings showed strong genetic influences on individual differences in local processing. All other cognitive factors showed low genetic influences. In addition, substantial non-shared environmental influences on individual differences were found for all cognitive factors, with variation in theory of mind ability being almost exclusively due to the non-shared environment.

There was also limited support that there is genetic overlap between cognitive domains and ASD. There was a modest genetic contribution to the covariance of global processing and ASD, with the phenotypic correlation derived from shared genetic effects. The negative correlation suggests that some genetic factors that decrease global processing ability also tend to increase liability to ASD. In addition, most of the phenotypic correlation between executive function and ASD could be explained by shared genetic effects. However, both of these results were not significant.

There has been one twin study of central coherence previously investigating whether certain cognitive abilities are endophenotypes of eating disorders in adult females, although the study did not use structural equation modelling (Kanakam, et al., 2013). The current results were similar to Kanakam, et al. (2013) as both studies found that within-pair correlations for MZ twins were double that of DZ twin for both local and global processing. Kanakam, et al. (2013) used this result to suggest a genetic basis to central coherence. Previous studies into the BAP have also suggested that local processing may have a genetic basis (Happé, et al., 2001). The

current study used structural equation modelling to support these previous findings and showed that the majority of the variance in local processing was due to genetic effects and one-third of the variance in local processing was due to the non-shared environment. However, only 6% of the variance in global processing was due to genetic effects, with 88% of the variance due to non-shared environmental effects. Kanakam et al (2013) preliminary conclusions that central coherence has a genetic basis were supported in the current sample for local processing only.

Previous studies into the aetiology of executive functions have suggested a moderate influence of the non-shared environment. Malone and Iacono (2002) investigated the aetiology of an aspect of executive function (inhibitory control) in a typically-developing group and found similar results with a higher influence of genetic effects than the current study (.57), but a significant moderate effect of the non-shared environment (.43). Conversely, Friedman, et al. (2008) investigated three executive functions (inhibition, working memory and set-shifting) in a typically-developing group and found that executive functions were influenced by a common genetic factor, which is highly heritable (99%). Set-shifting did have small but significant (13%) non-shared environmental influences. Looking at their model in more depth, it appears that non-executive variance in individual tasks had significant non-shared environmental effects (37-69%). All but one of the individual tasks showed no genetic influence (0-19%). These results are in line with the current results that there is no genetic influence (.05) but large non-shared environmental effects (.80) for executive function. This suggests that there is a need to account for the non-executive variances inherent within cognitive tasks to ensure that tasks measure what they are purported to measure since the variance attributed to non-shared environmental twin models includes the error component. The large effect of the non-shared environment in variance in the cognitive domains could be due to measurement error, such as not understanding the experimental instructions.

In addition, nearly all of the variance in theory of mind was due to non-shared environment effects (95%). In contrast, Hughes and Cutting (1999) found that two-thirds of the variance in theory of mind at age 3 was due to genetic effects, and only a third was due to the non-shared environment. A further study by Hughes, et al. (2005) suggested no genetic influence and moderate shared (.45) and non-shared (.66) environmental influences on theory of mind ability in 5-year-old children. The difference between the two studies was suggested to be due to the

sample, as there was insufficient power to detect the influence of the shared environment and the children were from very low SES families in the first study (Hughes & Cutting, 1999). There is potentially insufficient power in the current study to detect shared environment influences also, which may account for the non-significant results for the shared environment. Together, the current study and Hughes, et al. (2005) suggest a large role for the non-shared environment in the aetiology of theory of mind ability. The non-shared environment includes child-specific life events, such as sibling, parent and peer relationships. In particular, the non-shared environment may influence theory of mind ability through the social environment, as theory of mind development has previously been found to be linked to social abilities (Watson, Nixon, Wilson, & Capage, 1999). Furthermore, the negative correlation suggests that some environmental factors that decrease theory of mind ability also tend to increase liability to ASD. This supports the notion of a link between ASD and theory of mind ability that is perhaps mediated by the social environment as individuals with ASD have impairments in social interaction and social communication.

It was predicted that there would be genetic overlap between cognitive domains and ASD. Contrary to this prediction, local processing does not appear to be related to liability to ASD as there was no phenotypic correlation. This finding is contrary to past studies in which superior local processing has been found to be a characteristic of ASD. However, this finding is in line with Chapter 4 and 5 that found no significant difference between individuals with ASD and typically-developing controls in performance on measures of local processing and no difference on an overall local processing factor. In addition, Losh, et al. (2009) found no association between local processing and ASD. As already discussed, half of the phenotypic correlation between theory of mind and ASD could be explained by the common non-shared environment. In support of the prediction, most of the phenotypic correlation between executive functioning and ASD was due to common genetic effects (although non-significant). In addition, there was a strong (but non-significant) genetic correlation between global processing and ASD. The phenotypic correlation between global processing and ASD was also largely due to common genetic effects. A possible proposal from these results is that the same genes influence global processing/executive function and ASD, but there is not sufficient power within the current study to obtain significant results. However, global processing and executive functioning showed low

and non-significant genetic influence and so there would have been limited variance to partition into common and individual genetic effects.

One of the aims of the current study was to investigate if cognitive atypicalities could be possible cognitive endophenotypes in ASD. Previous studies have found that deficits in executive function characterised the endophenotype in ASD, particularly planning ability, but weak central coherence (local processing ability) and theory of mind deficits did not appear to be part of the cognitive phenotype (Nyden, et al., 2011). The current results support this previous study, with no phenotypic association between local processing, and no genetic overlap between theory of mind ability and ASD. Executive function did show a (non-significant) genetic overlap with ASD. Likewise, global processing showed a genetic overlap with ASD; a cognitive domain that was not investigated in Nyden, et al. (2011). However, cognitive atypicalities should show evidence of heritability to be useful endophenotypes (Doyle, et al., 2005), and neither executive function, nor global processing, showed genetic influences in the present analyses.

7.4.2 Strengths and Limitations

The SR study has many strengths; it is a large population-based study, with two stages of systematic screening and the inclusion of those across the whole ASD spectrum to gain a more complete picture of ASD. There are also a large number of ASD twins in comparison to previous studies. In addition, the SR study conducted in-person assessments to measure the three cognitive domains and so does not rely merely on parental questionnaire data.

Several limitations need to be considered when reflecting upon the results of the study. First, some potentially eligible families did not enrol in the SR study. Second, a main limitation of the current study is that of statistical power. The SR study attempted to recruit a sufficient number of MZ and DZ twin pairs concordant and discordant for ASD and a large number of MZ and DZ control twins, to be able to detect significant parameter estimates using genetic model-fitting. The 95% confidence intervals around estimates are large, reflecting that the number of twin pairs available for analysis may be less than the number needed to apply the bivariate statistical approaches. Although it would be difficult to increase the clinical sample of twins, one possibility to enhance power is to add data from a larger sample of typically-developing control twin pairs. Thirdly, the tasks may not have fully encapsulated the cognitive ability that they purport to

measure. For example, there is no single task/battery that can exhaustively measure all aspects of executive function, and tests of individual executive functions are rarely “process pure“. This could have led to the higher estimates of non-shared environment across the cognitive domains, which highlights potential measurement error. Other issues within the cognitive tasks used to assess the three cognitive domains could affect performance, such as not understanding the cognitive task, poor task instruction, poor motor execution (a deficit characteristic of ASD) and issues with response selection.

7.4.2.1 Assumptions and Limitations of the Twin Design

Five issues that affect twin modelling should be considered. Firstly, one of the main assumptions of the twin design is that the environment of MZ and DZ twins is equal – known as the ‘equal environments assumption’. This assumes that MZ twins are more similar than DZ twins for a certain trait because they share more genetic effects, not because MZ twins experience more similar environments than DZ twins. The validity of the equal environments assumption has been supported in previous studies (Kendler, Neale, Kessler, Heath, & Eaves, 1993).

Pre-natal factors may increase the similarity between MZ twins compared to DZ twins, independent of genetic effects. 70% of MZ twin pregnancies are monochorionic; the foetuses share both a placenta and a chorionic membrane (the outer membrane enclosing the foetus), but all DZ twin pregnancies and 30% of MZ twin pregnancies are dichorionic; the foetuses develop two separate chorions with half of dichorionic pregnancies sharing placentas and the other half having separate placentas. Monochorionic twins are at increased risk of pre- and post-natal complications. However, the effects of chorionicity on estimates of heritability of cognitive abilities are likely to be small.

The results from the twin sample need to be generalisable to the singleton population. A key difference between twins and singletons is the pre-natal environment. Twins have increased risk of pregnancy and birth complications, including foetal growth restriction, twin-to-twin transfusion syndrome, prematurity and low birth weights. For example, it has been found that low birth weight increases the risk for ASD (Schendel & Bhasin, 2008). Furthermore, it has been suggested that twinning itself may be a risk factor for ASD with a higher prevalence of ASD in twins (Greenberg, Hodge, Sowinski, & Nicoll, 2001). However, other studies demonstrate that

being a twin does not increase the risk of ASD (Curran et al., 2011; Hallmayer, et al., 2011; Hultman, Sparen, & Cnattingius, 2002).

An assumption of the twin design is that there is no effect of assortative mating on a trait. Assortative mating involves the process of non-random selection when choosing a mate, which occurs when an individual chooses a partner who has more traits in common with them. This would lead to an increased similarity between parents and offspring, as well as between DZ twins. Assortative mating would conceal non-additive genetic effects and inflate shared environment estimates because due to increased similarity of DZ twins. Assortative mating has been implicated in ASD (Constantino & Todd, 2005). However this result was based on spouse reports and a large population-based sample found no evidence of assortative mating for ASD (Hoekstra, et al., 2007).

Lastly, gene-environment correlation refers to the influence that genetic factors have on an individual's environment. The twin design assumes independence of genes and environment. It may therefore inflate heritability estimates because the genetics of MZ twins may influence their environment and therefore increase their similarity. Gene-environment interactions occur when the expression of an individual's genotype is dependent on their environment, and vice versa. If gene-environment correlations or interactions exist, then estimates of both genetic and environmental influences may be inflated.

7.4.3 Future Directions

Future studies should investigate age-related changes in genetic and environmental influences on individual differences in cognitive measures. The current study examined cognitive atypicalities in adolescence. However, it may be the case that genetic influences on cognitive atypicalities are more evident in earlier development, and environmental influences may be more important in later development. Therefore, longitudinal studies will be needed to examine the developmental pathways involved in cognitive atypicalities in ASD.

Further research could examine if the three cognitive domains that characterise ASD (theory of mind, weak central coherence, and executive function) share genetic influences or are largely genetically independent from one another. If phenotypic and genetic correlations between

different cognitive domains of ASD were low then this would support the claim that different cognitive substrates underlie different symptoms/features of ASD.

Lastly, the current study highlights the need to investigate what specific non-shared environmental influences might affect the development of individual differences in central coherence, executive functions, and theory of mind in ASD.

7.4.4 Conclusions

To summarise, this study explored the heritability of three cognitive domains (weak central coherence, executive function and theory of mind) that characterise ASD, and examined the genetic and environmental overlap between these cognitive domains and ASD using a twin sample. Global processing, executive function and theory of mind were modestly associated with ASD. Local processing showed strong genetic influence. All other cognitive domains showed low genetic influence and substantial non-shared environmental influences. Overall, there was limited support for the proposal that these cognitive atypicalities are useful endophenotypes of ASD.

Chapter 8 Trying to Make Sense of a Heterogeneous Disorder: A Factor Mixture Modelling Approach to Autism Spectrum Disorder

The clinical phenotype of autism spectrum disorder (ASD) is characterised by considerable heterogeneity, with individuals presenting with different patterns and severity of symptoms. Heterogeneity presents a challenge to research on aetiology and treatment; studies may be mixing 'apples and oranges'. This chapter therefore examined if more homogeneous behavioural subtypes of ASD could be identified as the fractionated theory recognises that this heterogeneity may be the unavoidable consequence of variation along different dimensions of impairment (Happé & Ronald, 2008).

8.1 Introduction

Despite sharing the diagnostic core features of impaired social-communication and restricted/repetitive behaviour (American Psychiatric Association, 2013), individuals with ASD show a wide manifestation of symptoms, varying in pattern and severity. This heterogeneity is considered a major hindrance in the study of the aetiology and treatment of ASD. Therefore, this study attempted to identify more homogeneous subgroups in ASD using a statistical modelling approach and to characterise these subgroups in terms of their patterns of comorbid difficulties.

Several studies have attempted to identify homogeneous subgroups of individuals with ASD using two different approaches to subgrouping; using clinical features or using statistical methods. With regards to clinical features, studies have tried to subgroup ASD using either a categorical or dimensional approach to ASD (see Beglinger & Smith, 2001, for a review on subgrouping in ASD).

Several studies have used statistical methods to identify homogeneous subgroups of individuals with ASD. Cluster analytic studies have derived up to four subgroups for ASD (see Wiggins, Robins, Adamson, Bakeman, & Henrich, 2012). These have largely distinguished subgroups by symptom severity, i.e., the degree of impairment on social and communication deficits, and restricted and repetitive behaviours and interests (RRBIs). Latent class analysis has also been

used. For example, Munson et al. (2008) used IQ to create subgroups and identified four classes within ASD; (1) low IQ, (2) low verbal/medium nonverbal IQ, (3) medium IQ, and (4) high IQ. Machine learning approaches have also been utilised. For example, Bruining et al. (2014) identified ASD behavioural signatures that were related to the genetic cause of ASD and found that signature phenotypes were familial and might be used to stratify cases of ASD.

Factor mixture modelling is an extension of latent class analysis and allows for severity variation within class. It allows for the integration of both categories (latent class analysis) and dimensions (confirmatory factor analysis) to identify more homogeneous subgroups. It has previously been used in two recent studies of ASD. Frazier, et al. (2012) examined approximately 15,000 siblings (9,000 ASD; 6,000 non-ASD) and identified a two-factor/two-class solution. The two classes corresponded to diagnosis, i.e., individuals with ASD were assigned to one class and those without an ASD diagnosis were assigned to a second class. Georgiades, et al. (2013) examined 391 children who had recently been diagnosed with ASD (aged 3- to 4-years-old) and identified a two-factor/three-class solution. The three classes were based on differential severity gradients on symptom dimensions. In addition to having different symptom severity levels, Georgiades and colleagues (2013) found that children from the subgroups were diagnosed at different ages and were functioning at different adaptive, language, and cognitive levels. In both studies, the two factors corresponded to a social/communication factor and an RRBI factor, supporting the structure of diagnostic criteria in DSM-5 (American Psychiatric Association, 2013).

Thus far, there has been a dearth of research exploring another source of heterogeneity within ASD, specifically that of associated features and comorbidity with other psychiatric conditions. Recent studies suggest high rates of comorbidity; for example, Simonoff, et al. (2008) reported that 71% of children with ASD met criteria for at least one current psychiatric disorder in their population-based sample. It was reported that 42% of children with ASD met criteria for an anxiety disorder, 30% met criteria for an oppositional or conduct disorder, and 1.4% met criteria for a depressive disorder. Furthermore, ASD and attention-deficit/hyperactivity disorder (ADHD) co-occur at high rates (Tureck, Matson, May, Davis, & Whiting, 2013), with 28% of children with a diagnosis of ASD also meeting diagnostic criteria for ADHD (Simonoff et al., 2008). Only one previous study has used latent class analysis (LCA) to investigate comorbidity within ASD (van der Meer et al., 2012). Due to the reported high comorbidity between ASD and ADHD, van der

Meer, et al. (2012) examined whether different ASD/ADHD symptom classes exist. The LCA analysis produced five classes; ADHD only, ADHD [+ASD], ASD [+ADHD], and two 'normal' classes.

The current study investigated the behavioural heterogeneity present within ASD and attempted to identify more homogeneous subgroups, examining heterogeneity in a population-based ASD twin sample. A considerable degree of heterogeneity was present within this sample as the twins diagnosed with ASD and their unaffected co-twin pairs covered the complete autism spectrum. The first aim was to identify homogeneous subgroups by employing a factor mixture approach using the diagnostic items from the ADI-R. It was predicted that the subgroups would be distinguished by symptom severity. Based on the work of Georgiades and colleagues (2013), it was also expected that a two-factor solution would fit the data best; one factor corresponding to social/communication deficits, and a second factor corresponding to RRBIs.

The second aim was to explore the similarities and differences between individuals assigned to each subgroup in terms of age, gender, diagnosis, co-occurring behavioural and emotional symptoms (including depression, anxiety, hyperactivity, and conduct problems), sensory abnormalities and cognitive abilities. It was predicted that the subgroups would differ in terms of symptom severity; with subgroups ranging from few impairments through to those with severe impairments. Due to this prediction, it was expected that subgroups would differ in terms of gender and diagnostic status. It was predicted that subgroups would differ in cognitive functioning. Furthermore, it was predicted that certain subgroups would show higher rates of concurrent behavioural and emotional symptoms.

8.2 Method

8.2.1 Participants

The study sample for these analyses was taken from the Social Relationships (SR) Study (Chapter 3), and consisted of 254 individuals (mean age 13.50 years; 177 males); 141 participants had a diagnosis of ASD (mean age 13.52 years; 120 males), 41 had a diagnosis of broad spectrum autism (mean age 13.40 years; 30 males), 73 were unaffected co-twins (mean age 13.50 years; 27 males). Four individuals with ASD, 1 with broad spectrum autism, and 1 co-twin did not complete the ADI-R, and were not included in the analyses.

8.2.2 Measures

8.2.2.1 Diagnostic Measures

The ADI-R (Lord, Rutter, & LeCouteur, 1994) is a gold-standard assessment tool for ASD and is conducted as a structured parent interview. The diagnostic algorithm for children aged 4 and above was used. A subset of 37 items is used to create a diagnostic algorithm with items scored from 0 (not present) to 2 (definitely present). Some items can be coded as a 3 and are recoded as a 2 for the algorithm scores. The algorithm scores were used for the FMM.

The ADOS (Lord et al., 2000) is a semi-structured observational gold-standard assessment for ASD. The current study used the total score from the three ADOS domains (social, communication and RRBI domains) as a severity measure.

8.2.2.2 IQ

General cognitive ability was assessed using the WASI (WASI) (Wechsler, 1999) to obtain an estimated score for verbal and performance IQ and a full IQ score. To include the low IQ individuals in the analyses, the 14 nonverbal children were given a provisional WASI full-scale IQ score of 49 (1 point below the lowest possible score on the WASI).

8.2.2.3 Cognitive Tasks

The full description of the cognitive tasks can be found in Chapter 3. Briefly, participants completed an extensive cognitive battery to measure central coherence, executive function and theory of mind ability, lasting approximately 2 hours and administered in a counterbalanced order. The cognitive tasks were chosen as they were deemed appropriate for the age range and ability level of the participants. The cognitive tasks provided a comprehensive assessment of a full range of cognitive abilities in individuals and are sensitive to cognitive deficits which have previously been described in individuals with ASD. The cognitive factors created in Chapter 5 were used for the present analyses.

8.2.3 Questionnaire Measures

Parents and the twin pairs were asked to complete a questionnaire booklet and the measures are described in Chapter 3. The same parent completed the questionnaire booklet for both

twins. The SDQ (Goodman, 1997) was used to index behavioural problems, and the subscales were used to index emotional symptoms, conduct problems, hyperactivity, peer problems, and pro-social behaviours. The SMFQ (Sharp, et al 2006) was used to index depression and the RCADS (Chorpita, et al 2000) was used to index anxiety. In addition, sensory abnormalities were identified using the SSP (McIntosh, Miller, Shyu, & Dunn, 1999).

8.2.4 Analyses

In this chapter, all twins were treated as singletons in the analyses. However, as the participants are twin pairs, adjustments needed to be made for non-independence of the data. The cluster command in MPlus was used to account for the non-independence of the data. Analyses were carried out in MPlus 7 (Muthén & Muthén, 1998-2011), IBM SPSS 20 and STATA 10.1 (StataCorp, 2007).

8.2.4.1 Factor Mixture Modelling

A series of latent class analyses and confirmatory factor analyses were conducted to inform factor mixture models. Factor mixture models are an extension of latent class analysis and are a relatively novel method used to investigate unknown population heterogeneity (see Lubke & Muthén, 2005, for a detailed description of FMMs). The factor mixture model (FMM) combines the latent class model and common factor model to stratify individuals into relatively more homogeneous subgroups. The latent class model clusters participants based on the observed items to model the unobserved population heterogeneity within the FMM. The latent class model produces a categorical outcome by clustering participants into classes. For FMMs, the number of latent classes is specified in advance. Within FMM, the common factor model investigates the common influences of the observed items by creating continuous latent variables called factors. The covariance between participants within a class for the observed items is modelled by specifying the regression path between the observed items and the underlying continuous latent factors. An advantage of FMMs is that the factor structure of a questionnaire is modelled using the common factor model so that the observed scores are separated into factor scores and a residual such that measurement error is taken into account.

During the model estimation, posterior class probabilities were calculated for each participant. For the best fitting model, factor scores and class membership were calculated for each

individual. Factor scores were calculated based on the mean of the items that loaded on to each factor. On the basis of their highest probability, participants were assigned to their most likely class membership. Individuals could only belong to one class. The most likely class membership was then used for post-hoc analyses due to the recommendations of Clarke and Muthén (2009) that using most likely class membership is the best performing method (over other techniques, such as weighted-regression) when the entropy of the model is 0.80 or greater. It is suggested to use a more stringent criterion than the 5% level, and so a *p*-value of .01 was used. The post-hoc analyses used a series of multinomial logistic regressions to characterise classes (see Appendix 4), as parametric tests could not be used due to class membership being a discrete variable.

8.3 Results

8.3.1 Statistical Models

A total of four FMMs were tested using the raw subscale scores of the 37 ADI-R items. To guide the choice of the number of classes and factors for the FMM, six LCA models (one-to-six classes) and three CFA models (one-to-three factors) were also carried out. The two-factor CFA and the two-factor FMM forced the 29 ADI-R items that measure abnormalities in reciprocal social interaction and communication to load only on to a social-communication (SC) factor, and eight ADI-R items that measure restricted, repetitive, and stereotyped patterns of behaviours to load only on to an RRBI factor. Similarly, the three-factor CFA and the three-factor FMM forced the 16 ADI-R items that measure abnormalities in reciprocal social interaction to load on to a social factor, 13 ADI-R items that measure abnormalities in communication to load on to a communication factor, and the eight ADI-R items to load on to an RRBI factor. The LCA and CFA were also compared to the final FMM to assess whether the final FMM was a better overall fit to the data. The fit of all models was tested using established goodness-of-fit criteria such as Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC), and the Sample Size Adjusted Bayesian Information Criteria (SSA BIC) (Table 8.1). Lower values of AIC, BIC and SSA BIC indicate better model fit, with preference given to SSA BIC based on suggestions by Nylund, Asparouhov, and Muthén (2008). Furthermore, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test is reported, which examines if an additional class significantly improves the model (Lo, Mendell, & Rubin, 2001).

The LCA was based on fit and revealed a solution with five classes. Five classes had the best fitting adjusted BIC. Based on this outcome, the FMMs contained five classes. Direct statistical comparisons based on goodness-of-fit criteria revealed a "one-factor, five class" FMM solution to best fit the data. However, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test revealed that a two-class solution was preferred to a one-class solution (p = .044). In addition, the best-fitting CFA model revealed a two factor solution indicating that two factors may be more consistent with the data. Furthermore, previous research has also demonstrated a two-factor solution to ADI-R data, using a social-communication factor and an RRBI factor (Georgiades, et al., 2013). Taking this into consideration, a "two-factor, five-class" FMM was decided upon as the most comprehensive fit to the data. According to this FMM, individuals could be classified into five relatively homogeneous classes (Class 1: 23%, Class 2: 18%, Class 3: 17%, Class 4: 29%, Class 5: 13%, of the sample)[1].

[1] It is worth noting that the SSA BIC is marginally better for the five-class LCA compared to the two-factor/five-class FMM model. However, the free parameters for the five-class LCA was considerably more than for the two-factor/five-class FMM model (374 vs. 121), therefore implying that the two-factor/five-class FMM model is a more parsimonious fit to the data compared to the five-class LCA.

Table 8.1. LCA, CFA and FMM models, model fit indices, and class percentages (*N* = 249)

	Classes (c) or factors (f)	Log Likelihood	Number of Free Parameters	Entropy	AIC	BIC	SSA BIC	VLMR (p-value)	Class Percentages
LCA models	1c	-8782.889	74	-	17713.78	17975.25	17740.66	-	100%
	2c	-7035.352	149	.99	14368.71	14895.18	14422.82	< .001	44%, 54%
	3c	-6595.719	224	.99	13639.44	14430.92	13720.80	.760	16%, 44%, 40%
	4c	-6403.369	299	.99	13404.74	14461.22	13513.34	.760	22%, 32%, 12%, 34%
	5c	-6294.293	374	.97	13336.59	14658.07	13472.43	.696	12%, 24%, 22%, 17%, 25%
	6c	-6241.33	449	.98	13380.66	14967.15	13543.74	.800	11%, 5%, 15%, 21%, 16%, 32%
CFA models	1f	-9091.37	111	-	18404.74	18796.95	18445.06	-	
	2f	-9069.979	112	-	18363.96	18759.7	18404.64	-	
	3f	-9068.574	114	-	18365.15	18767.95	18406.55	-	
FMMs	1f 5c	-6597.342	118		13430.68	13847.62	13473.54	-	13%, 18%, 22%, 27%, 19%
	2f 5c	-6595.219	121		13432.44	13859.98	13476.39	.044	18%, 23%, 13% 17%, 29%
	3f 5c	-6616.183	124		13480.37	13918.51	13525.40	.256	12%, 32%, 32%, 4%, 20%
	4f 5c	-6478.108	129		13214.22	13670.02	13261.07	.175	22%, 32%, 11%, 3%, 32%

Notes: The best fitting models from a direct comparison across all goodness-of-fit criteria is presented in bold. AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; c = class; CFA = confirmatory factor analysis; f = factor; FMM = factor mixture model; LCA = latent class analysis; SSA BIC = Sample Size Adjusted Bayesian Information Criteria; VLMR = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test.

8.3.2 Symptom Profile of Classes

To assess qualitative differences between classes, mean scores for each ADI-R item were computed and these symptom profiles of the classes are shown in Figure 8.1. Additionally, Figure 8.2 represents the between- and within-class variability for ASD symptoms in a two-dimensional convex hull plot. It is notable that individuals in Class 4 had severe social-communication impairments, but a varying degree of RRBI impairments.

Table 8.2 shows the mean symptoms scores across classes for symptom factors, and the ADOS. Mean factor sum scores for social-communication factor and RRBI factor were computed using the appropriate ADI-R items, corresponding to the two factors used in the FMM. The social-communication factor and RRBI factor were significantly correlated in the participants with a broad spectrum diagnosis (r = .57, p < .001) and ASD (r = .66, p < .001), but were not correlated for the unaffected co-twins (r = .07, p = .577). Additionally, the SC and RRBI factors were only correlated in Class 5 (r = .37, p < .05; all other classes: r < .20, p > .091). A Fisher's r-to-z transformation was used to test if the correlation for Class 5 was significantly different to the other classes. The correlation between Class 2 and 5 was marginally significant (z = 1.57, p = .058) and all other comparisons were not significant (p > .131). A series of multinomial logistic regressions comparing severity of ASD symptoms across class membership revealed that the five classes differed significantly on both the SC factor (all ps < .001) and the RRBI factor (all ps < .008), with one exception: no significant difference between RRBIs factor score for Class 1 and Class 2 (p = .135). Overall, the severity of ASD symptoms (as measured by the ADOS) differed across most classes (all ps < .001), with one exception: Class 2 and Class 3 (p = .141) did not differ in overall symptom severity. ADOS social impairments did not differ significantly when comparing Class 3 with Class 2 (p = .040) or Class 4 (p = .023). All other class comparisons for ADOS social symptoms were significant (all ps < .01). ADOS communication impairments did not differ significantly when comparing Class 2 with Class 3 (p = .108). All other class comparisons for ADOS communication symptoms were significant (all ps < .001). Class 5 had significantly higher ADOS RRBI scores than all other classes (all ps < .001). Furthermore, Class 4 had significantly higher ADOS RRBI scores than Class 1 (p < .001), and marginally significantly higher than Class 2 (p = .011) and Class 3 (p = .015).

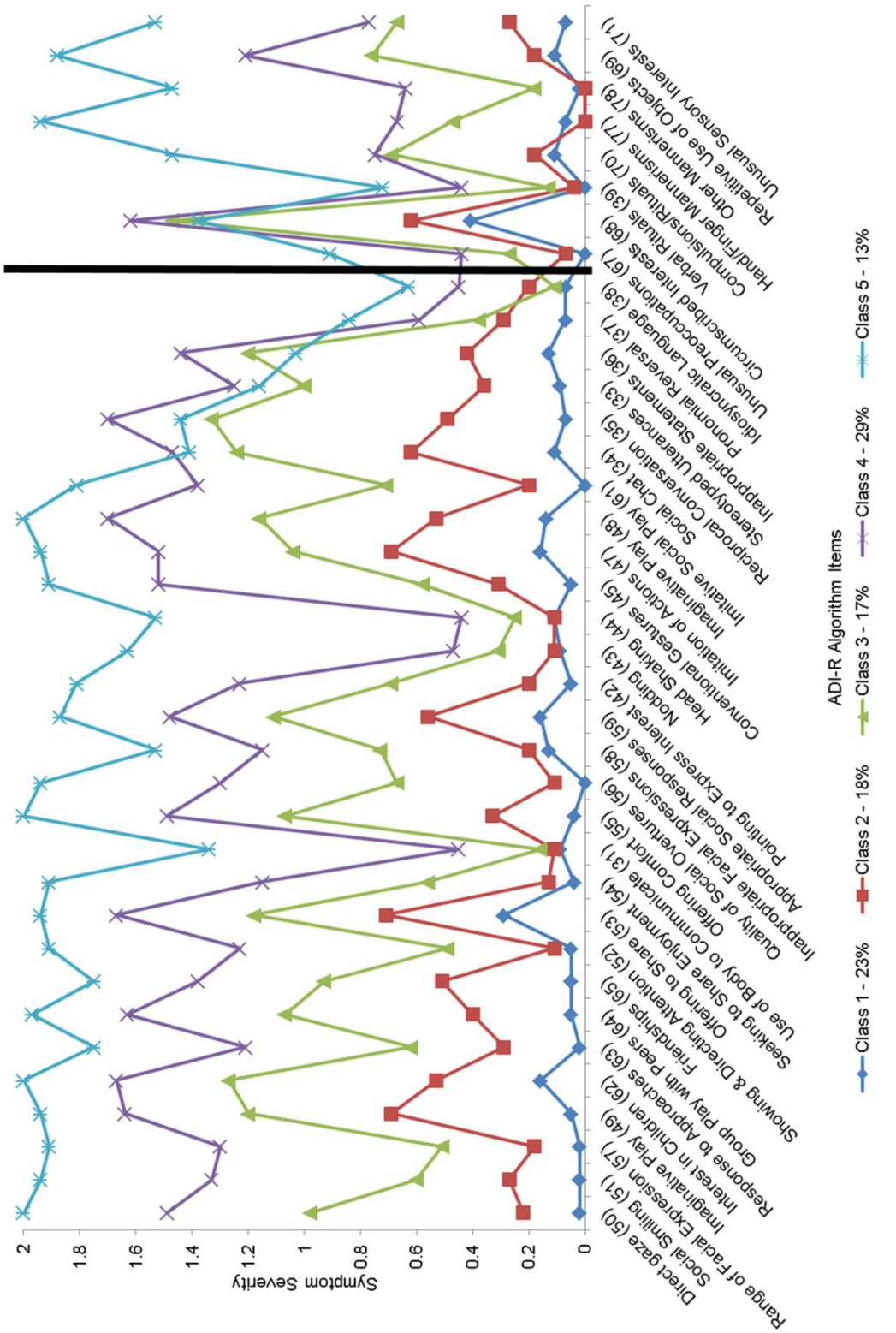


Figure 8.1. Symptom profiles for the five classes for the factor mixture model with “two factors, five classes” (*N* = 249).

Notes: The horizontal axis represents the diagnostic algorithm items from the ADI-R. The vertical axis represents the average item score (minimum = 0, maximum = 2) with a higher score reflecting more severe deficits. The line indicates the distinction between the items loading on to the SC factor (left) and the items loading on to the RRBI factor (right).

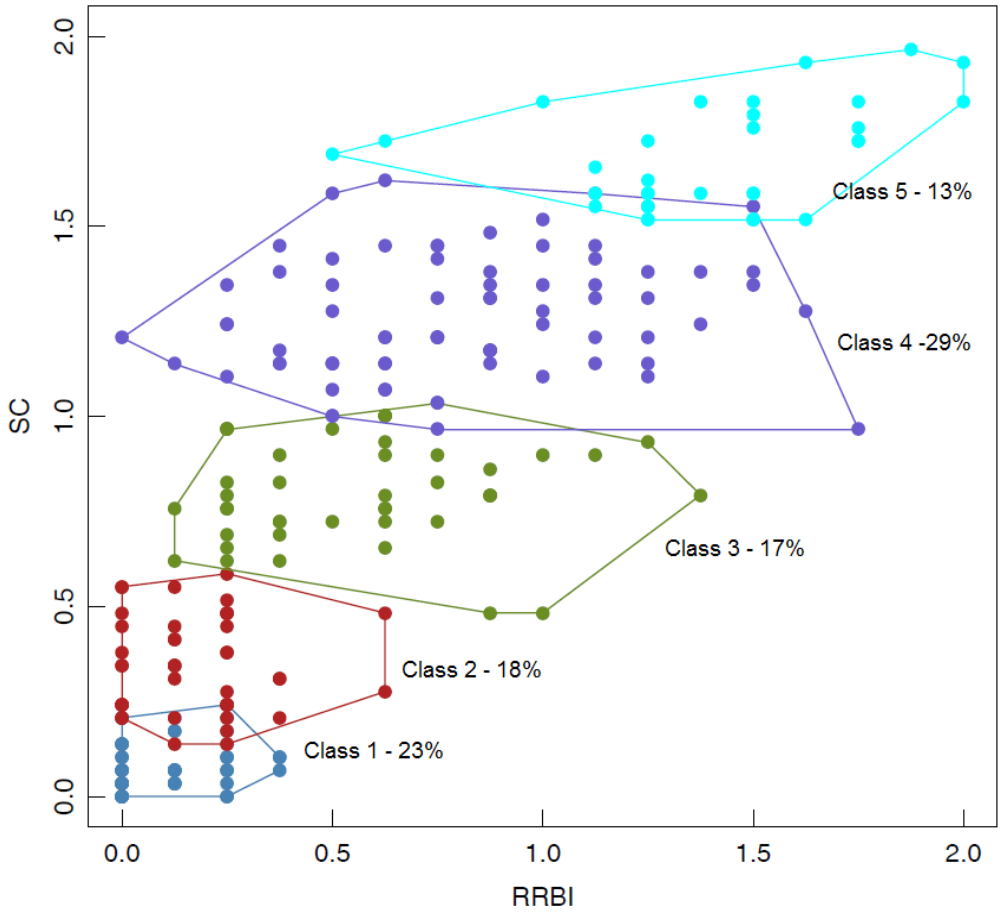


Figure 8.2. Social-communication (SC) factor by RRBI factor two-dimensional convex hull plot for the five classes (*N* = 249).

Table 8.2. Characterisation of classes based on age, gender, diagnosis, IQ, and symptom scores

Mean (SD)	Class 1	Class 2	Class 3	Class 4	Class 5	Group Differences
N (%)	56	45	43	73	32	
Age	13.53 (0.66)	13.33 (0.62)	13.64 (0.62)	13.51 (0.77)	13.37 (0.65)	n.s.
Gender	22M; 34F	23M; 22F	9F; 34M	3F; 70M	7F; 25M	1 = 2, 3 = 5 4 M> 1, 2, 3, 5 1, 2 F> 3, 4, 5
Diagnosis (N)	50CT; 4BSP; 2ASD	20CT; 17BSP; 8ASD	2CT; 14BSP; 27ASD	0CT; 5BSP; 68ASD	0CT; 0BSP; 32ASD	1 ≠ 2 ≠ 3 ≠ 4 ≠ 5
VIQ	103.64 (14.50)	102.09 (16.23)	94.60 (18.49)	89.93 (18.99)	69.24 (9.18)	1, 2 > 4, 5 1-4 > 5
PIQ	103.25 (14.54)	102.84 (15.54)	97.33 (17.67)	97.99 (19.39)	75.36 (16.68)	1-4 > 5
FIQ	103.82 (13.24)	102.67 (15.91)	95.34 (17.79)	92.83 (19.80)	70.75 (23.72)	1-4 > 5 1, 2 > 4, 5
SC factor	0.08 (0.07)	0.34 (0.12)	0.80 (0.14)	1.27 (0.16)	1.68 (0.14)	5 > 4 > 3 > 2 > 1
RRBI factor	0.10 (0.12)	0.17 (0.16)	0.57 (0.31)	0.82 (0.38)	1.41 (0.34)	5 > 4 > 3 > 2, 1
ADOS total	2.85 (3.99)	5.89 (4.80)	7.43 (4.32)	11.41 (5.96)	17.74 (5.92)	5 > 4 > 3, 2 > 1

Notes: ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; BSP = broad spectrum; CT = unaffected co-twin; F = female; FIQ = full scale intelligence quotient; M = male; N = number of participants; PIQ = performance intelligence quotient; SC = social-communication; VIQ = verbal intelligence quotient

8.3.3 Characterisation of Classes

The distribution of all individuals across the distinct classes, as well as the age, gender, diagnosis, and IQ characteristics of each class are provided in Table 8.2. The series of multinomial logistic regressions comparing age across class membership revealed that age did not differ significantly between classes (all *p*s > .031). Class 1 and 2 ($p = .236$), and Class 3 and 5 ($p = .921$) had similar proportions of males and females. However, there were a significantly higher proportion of females in Classes 1 and 2 compared to Class 3, 4 and 5 (2 vs. 5 marginally significant $p = .018$). Furthermore, Class 4 had a significantly higher proportion of males than all other classes (all *p*s < .01).

In terms of diagnostic status across class membership, there was a significant difference in distribution by diagnosis (i.e., unaffected co-twin, broad-spectrum, or ASD diagnosis) across the five classes (all *p*s < .001). Class 1 contained proportionally more individuals without a diagnosis of ASD (i.e., unaffected co-twin; 89%). Class 5 comprised only individuals with an ASD diagnosis. The greatest proportion of broad-spectrum diagnoses was within Class 2 (38%) and Class 3 (33%).

Class 1 had a significantly higher VIQ than Class 4 ($p = .008$) and Class 5 ($p < .001$). Class 2 had a significantly higher VIQ than Class 4 ($p = .003$) and Class 5 ($p < .001$). Overall, Class 5 had a significantly lower VIQ than all other classes (all *p*s ≤ .001). PIQ did not differ significantly across Class 1 to 4 (all *p*s > .269). However, Class 5 had a significantly lower PIQ than all other classes (all *p*s ≤ .001). Class 5 had a significantly lower full-scale IQ than all other classes (all *p*s < .001).

In addition, the class concordance rate was 48% for monozygotic twins compared to only a 5% concordance rate for dizygotic twins.

8.3.4 Cognitive Profiles

The cognitive factors created in Chapter 5 were used for these analyses. To reiterate, all cognitive tasks were subject to an exploratory factor analysis, with a four factor solution fitting the data the best. These results were used to create four cognitive composites, each reflecting a different aspect of cognition. These cognitive composite scores were then standardised to

create the final factor scores. A series of multinomial regressions were then used to characterise classes by cognitive factor.

Figure 8.3 presents the cognitive profiles of the five classes. Class 4 (*M* = -1.13) and Class 5 (*M* = -1.14) performed worse than Class 1 on the executive function factor (*M* = -0.33, *p* < .01). On the theory of mind factor, Class 4 (*M* = -1.04) performed significantly poorer than Class 1 (*M* = -0.04, *p* = .002), Class 2 (*M* = 0.19, *p* = .001), and marginally poorer than Class 3 (*M* = -0.26, *p* = .026). On the global processing factor, Class 3 (*M* = -0.64) and Class 4 (*M* = -0.59) performed significantly poorer than Class 1 (*M* = 0.08, *p*s < .005). All other class comparisons were non-significant (all *p*s > .054).

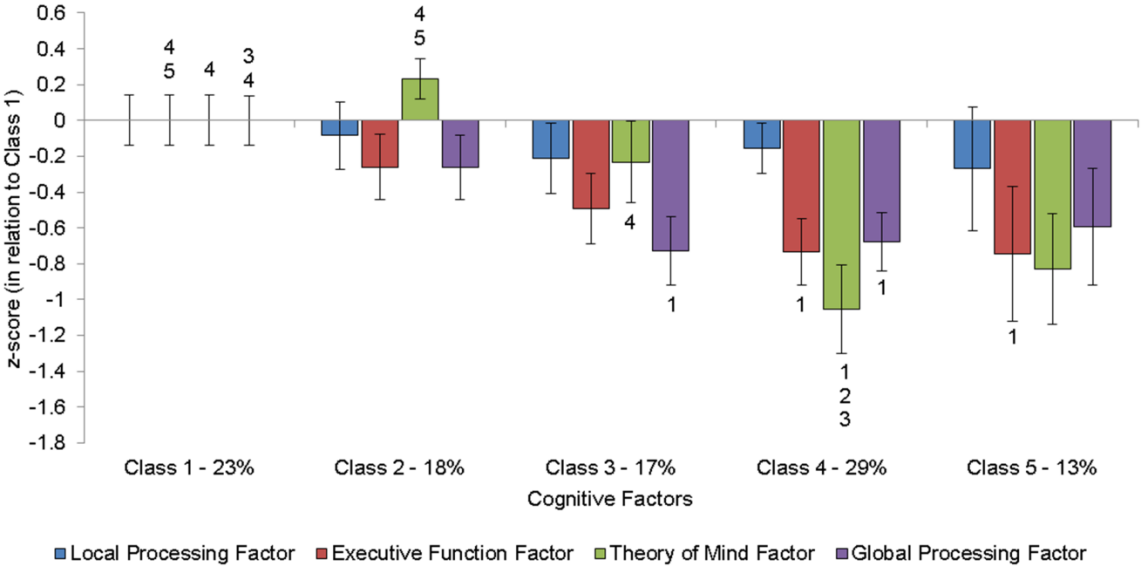


Figure 8.3. Performance on cognitive factors by five classes, after accounting for IQ (*N* = 153).

Note: Scores are presented as z-scores (relative to a control group). Error bars are standard errors. Numbers above bars indicate class numbers (i.e., 1 = Class 1). A number above a bar indicates a significant difference between the class that the bar represents and the class indicated by the number above the bar (*p* < .01).

8.3.5 Concurrent Behavioural Symptom Profiles of Classes

8.3.5.1 Rater Agreement

The correlations between the parent and child ratings for each questionnaire are shown in Table 8.3. Table 8.3 indicates that across all participants, the parent and child reports are significantly correlated. However, a varying pattern of results emerged when considering the cross-rater correlations separated by most likely class membership. For correlations between parent and

child report for SDQ Total Difficulties, cross-rater correlations were significant for Class 1, 2 and 3 only, with non-significant correlations for Class 4 and 5. A differing pattern of cross-rater correlations emerged across SDQ subscales. For correlations between parent and child reports for SMFQ Depression, cross-rater correlations were significant for Class 2 and 3, with non-significant correlations for Class 1, 4 and 5. For correlations between parent and child reports for RCADS Anxiety, cross-rater correlations were significant across all classes.

Table 8.3. Correlations between parent-report and child-report versions of questionnaires, by most likely class membership

Questionnaire Measure	All	Class 1	Class 2	Class 3	Class 4	Class 5
SDQ Total Difficulties	**.55*** **	**.42** **	**.67*** **	**.64*** **	.25	.42
SDQ Emotional Symptoms	**.40*** **	.13	**.70*** **	**.52** **	.23	**.26** **
SDQ Conduct Problems	**.47*** **	**.33** *	**.67*** **	**.78*** **	**.59*** **	.17
SDQ Hyperactivity	**.49*** **	**.57*** **	**.48** **	**.47** **	.24	**.57*** **
SDQ Peer Problems	**.66*** **	**.55*** **	**.43** *	.33	**.52*** **	**.50*** **
SDQ Pro-social Behaviour	**.37*** **	.30	.32	**.44** *	**.35** *	.16
SMFQ Depression	**.49*** **	.13	**.81*** **	**.57** **	.22	.10
RCADS Anxiety	**.44*** **	**.56*** **	**.48*** **	**.43** *	**.53*** **	**.33*** **

Note: *p < .05; **p < .01; ***p < .001

8.3.5.2 Self-Report Measures

Figure 8.4 shows the standardised mean scores across self-report measures in relation to the mean and standard deviation of Class 1. Class 5 rated their behavioural problems (SDQ total difficulties score) similarly to all other classes (all ps > .050). Class 4 (M = 15.27) rated their behavioural problems significantly higher than Class 1 (M = 10.80, p = .001) and Class 2 (M = 11.19, p = .003). Class 3 (M = 0.77) rated their behavioural problems marginally higher than Class 1 (M = 10.80, p = .011). The ratings for SDQ subscales (hyperactivity, emotional problems, conduct problems, peer problems, pro-social behaviour) did not significantly differ across most likely class membership (all ps > .110). Furthermore, the ratings for anxiety and depression did not significantly differ across most likely class membership (all ps > .048).

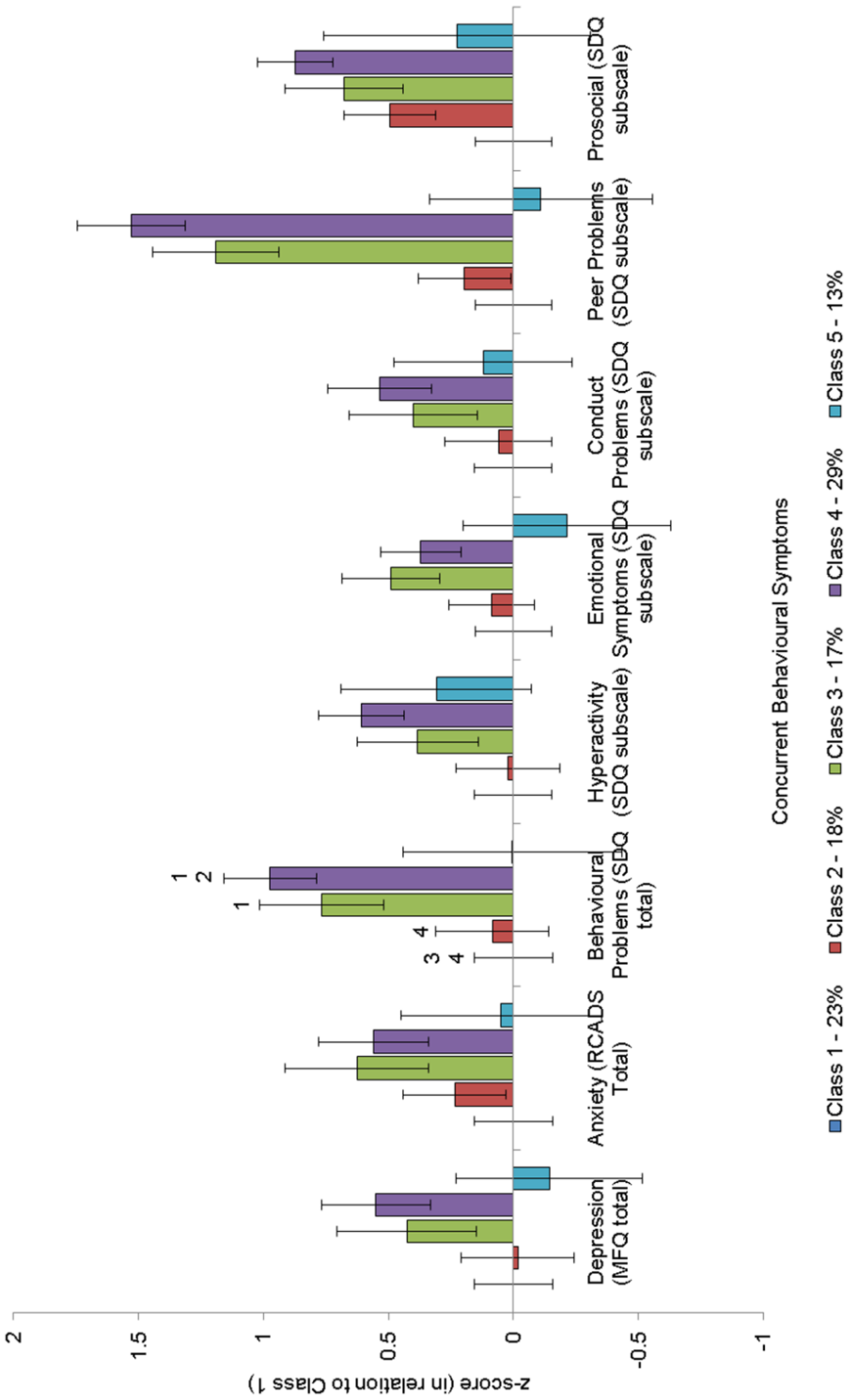


Figure 8.4. Concurrent behavioural symptom profiles across classes for self-report measures, relative to Class 1.

Notes: Higher values indicate more severe symptoms (Prosocial subscale is reversed). Numbers above bars indicate class numbers (i.e., 1 = Class 1). A number above a bar indicates a significant difference between the class that the bar represents and the class indicated by the number above the bar ($p < .01$). MFQ = Mood and Feelings Questionnaire; RCADS = Revised Children's Anxiety and Depression Scale; SDQ = Strengths and Difficulties Questionnaire.

8.3.5.3 Parent Report Measures

Table 8.4 reports the mean scores across the parent-report measures for each class. Figure 8.5 and Figure 8.6 show the standardised mean scores across parent-report measures in relation to the mean and standard deviation of Class 1 and indicates significant differences between classes. Figure 8.5 shows that Classes 3, 4, and 5 have significantly higher depression and anxiety ratings than Class 1, and significantly more overall behavioural problems and peer problems than Classes 1 and 2. In addition, Classes 2, 3, 4, and 5 have significantly more emotional problems and conduct problems than Class 1. Figure 8.6 indicates that Class 1 and 2 have few sensory abnormalities, Class 3 has intermediary sensory abnormalities, and Class 4 and 5 have significantly more overall sensory abnormalities than other classes.

Table 8.4. Class means based on concurrent behavioural profiles

	Class 1	Class 2	Class 3	Class 4	Class 5
SDQ					
Emotional Symptoms	1.32	3.12	4.48	4.16	3.32
Conduct Problems	0.78	1.73	2.26	2.44	2.15
Hyperactivity	2.43	3.25	4.75	6.31	6.81
Peer Problems	0.85	1.97	4.50	5.36	6.36
Prosocial Behaviour	8.88	7.94	7.22	5.38	3.18
Total Difficulties	5.26	9.91	16.23	18.28	18.58
Anxiety					
RCADS Total	16.16	21.26	24.33	26.58	27.85
Depression					
MFQ Total	1.55	2.72	4.75	5.21	4.19
Sensory Behaviours					
SSP Total	15.01	22.58	31.15	45.97	62.50

Note: Significant group differences are shown in Figure 8.5 and Figure 8.6

Table 8.5 shows the numbers and percentages of participants within each class who are below/above defined cut-offs for each parent-report measure. Table 8.5 shows that no individuals assigned to Class 1 had abnormal rates of behavioural difficulties. This percentage increased Class 2 (13%) with 42% of individuals in Class 3 showing abnormal rates of behavioural difficulties. Over half of individuals assigned to Classes 4 and 5 displayed abnormal rates of behavioural difficulties. Table 8.5 also indicates increasing rates of abnormal rates of hyperactivity from individuals assigned to Class 1 (0%) through to Class 4 (49%) and Class 5 (57%). In addition, just 5% of Class 1 had abnormal rates of peer problems. The rates of peer problems increased to 21% for Class 2 and increased considerably to 81% for Class 3, with nearly all individuals in Class 5 (95%) showing abnormal rates of peer problems. Furthermore, according to Table 8.5, 29% of Class 1 met cut-off criteria for depression, which increased to 41% of Class 5. 36% of Class 1 met cut-off criteria for anxiety, which increased to 56% of individuals in Class 3 and 53% of individuals in Class 5.

Table 8.5. Number and percentages of participants above and below cut-offs for concurrent behavioural symptoms, by class membership.

Parent Report Measures	Class 1		Class 2		Class 3		Class 4		Class 5	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
SDQ Total Difficulties										
Normal	38	(97)	26	(81)	11	(35)	12	(21)	3	(16)
Borderline	1	(3)	2	(6)	7	(23)	12	(21)	4	(21)
Abnormal	0	(0)	4	(13)	13	(42)	33	(58)	12	(63)
SDQ Emotional Symptoms										
Normal	38	(93)	15	(46)	16	(52)	25	(43)	11	(50)
Borderline	2	(7)	12	(36)	1	(3)	8	(14)	3	(14)
Abnormal	0	(0)	6	(18)	14	(45)	25	(43)	8	(36)
SDQ Conduct Problems										
Normal	39	(98)	24	(73)	23	(74)	34	(58)	13	(65)
Borderline	1	(2)	3	(9)	1	(3)	8	(13)	2	(10)
Abnormal	0	(0)	6	(18)	7	(23)	17	(29)	5	(25)
SDQ Hyperactivity										
Normal	35	(88)	26	(81)	19	(59)	23	(39)	5	(24)
Borderline	5	(12)	1	(3)	5	(16)	7	(12)	4	(19)
Abnormal	0	(0)	5	(16)	8	(25)	29	(49)	12	(57)
SDQ Peer Problems										
Normal	35	(85)	19	(58)	5	(16)	6	(10)	1	(5)
Borderline	4	(10)	7	(21)	1	(3)	8	(14)	0	(0)
Abnormal	2	(5)	7	(21)	26	(81)	44	(76)	21	(95)
SDQ Pro-social Behaviours										
Normal	38	(93)	30	(91)	26	(81)	27	(47)	4	(18)
Borderline	1	(2)	1	(3)	4	(13)	10	(17)	4	(18)
Abnormal	2	(5)	2	(6)	2	(6)	21	(36)	14	(64)
SMFQ Depression										
Below cut-off	40	(71)	30	(67)	26	(60)	45	(62)	19	(59)
Above cut-off	16	(29)	15	(33)	17	(40)	28	(38)	13	(41)
RCADS Anxiety										
Below cut-off	34	(61)	26	(58)	18	(42)	36	(50)	12	(38)
Subclinical	2	(3)	2	(4)	1	(2)	4	(5)	3	(9)
Above cut-off	20	(36)	17	(38)	24	(56)	33	(45)	17	(53)

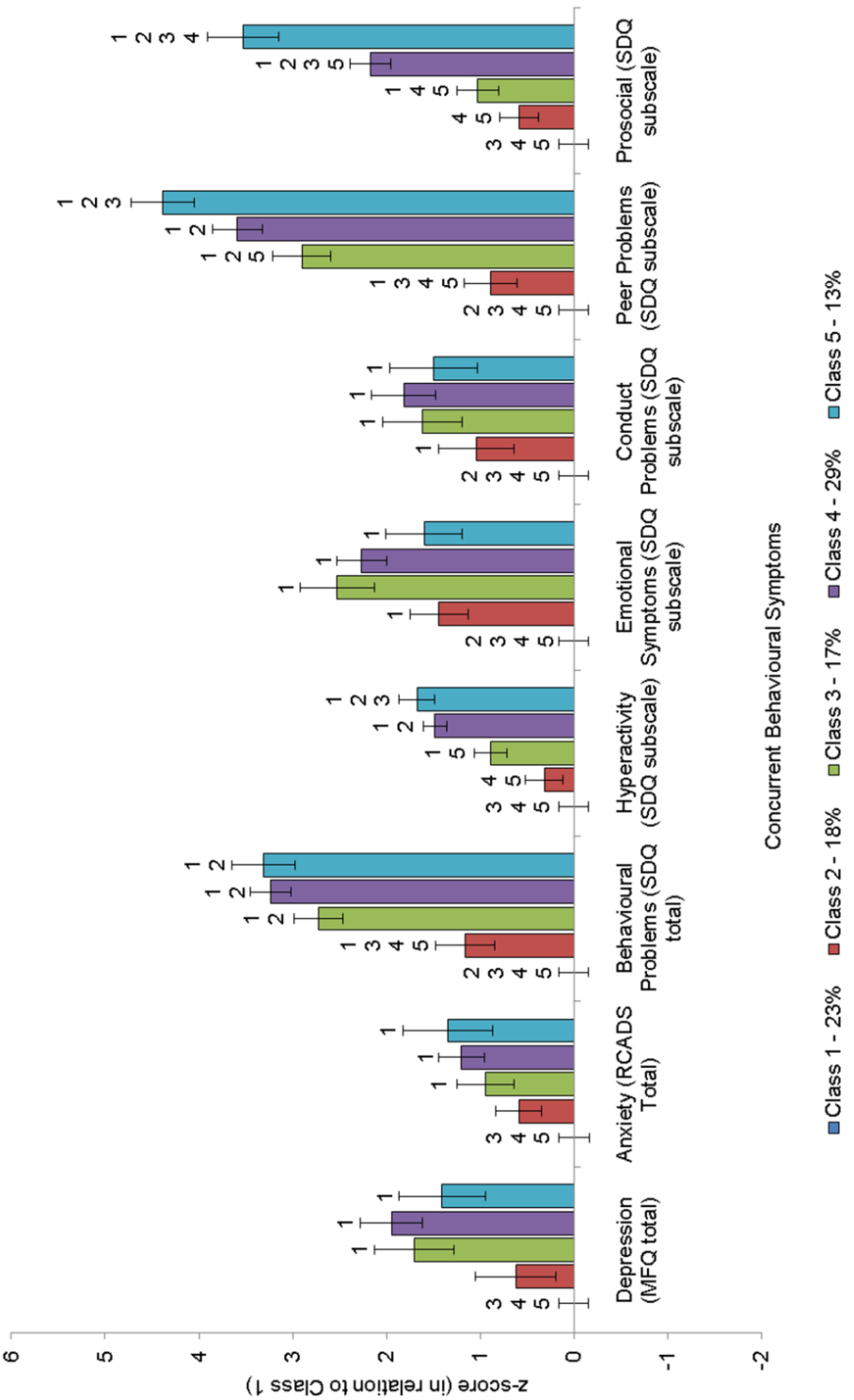


Figure 8.5. Concurrent behavioural symptom profiles across classes for parent-report measures, relative to Class 1.

Notes: Higher values indicate more severe symptoms (Prosocial subscale is reversed). Numbers above bars indicate class numbers (i.e., 1 = Class 1). A number above a bar indicates a significant difference between the class that the bar represents and the class indicated by the number above the bar ($p < .01$). MFQ = Mood and Feelings Questionnaire; RCADS = Revised Children's Anxiety and Depression Scale; SDQ = Strengths and Difficulties Questionnaire.

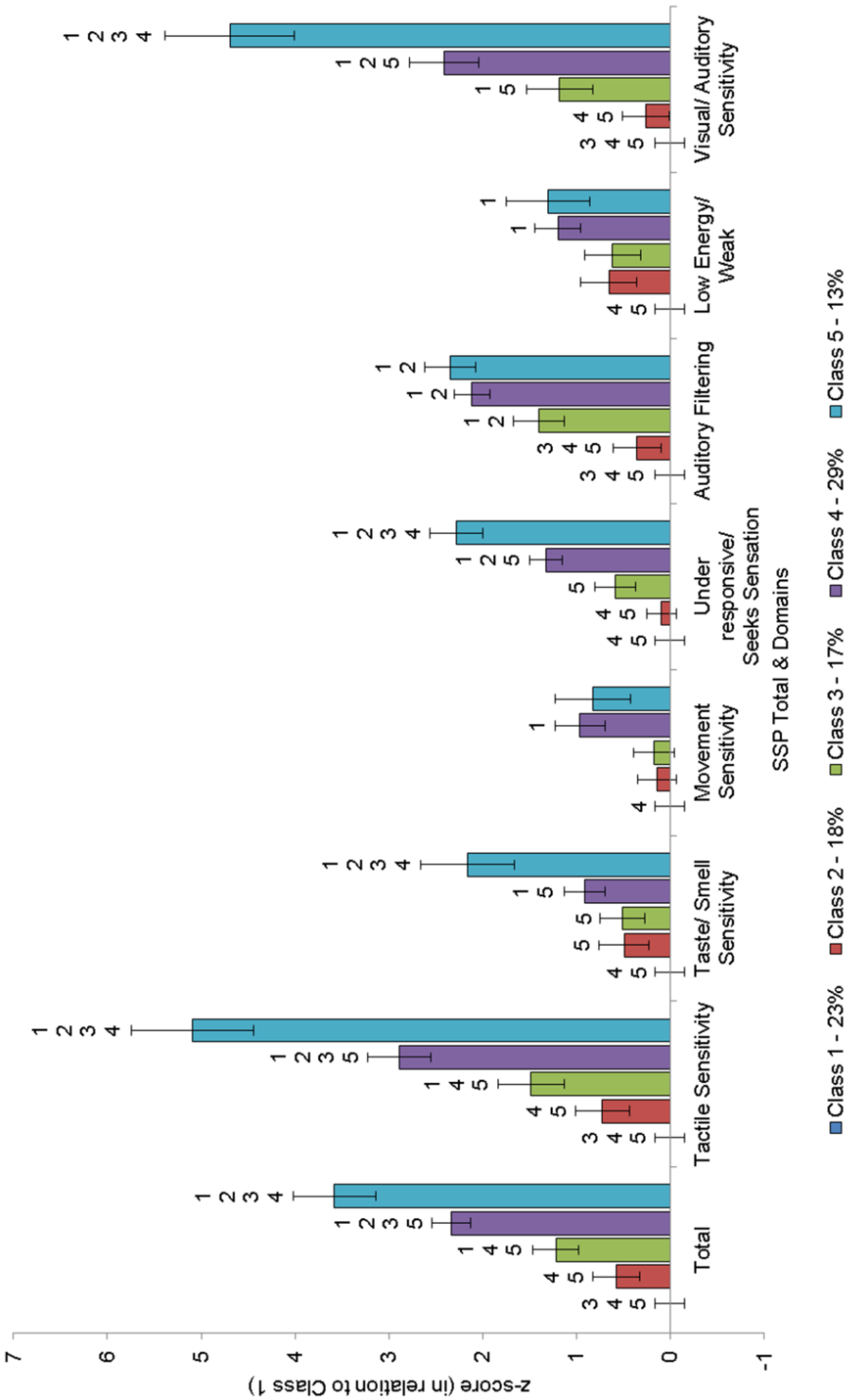


Figure 8.6. Sensory profiles across classes for the Short Sensory Profile (SSP), relative to Class 1.

Notes: Higher values indicate greater sensory abnormalities. A number above a bar indicates a significant difference between the class that the bar represents and the class indicated by the number above the bar ($p < .01$)

8.4 Discussion

8.4.1 Summary of Findings

The first aim of this study was to identify more homogeneous subgroups within ASD by using a factor mixture approach using the diagnostic items from the ADI-R. This approach produced a "two-factor, five class" FMM model, as having the most comprehensive fit to the data. According to this model, twins from pairs with at least one diagnosed ASD individual could be assigned to one of five relatively homogeneous classes based on their social-communication and RRBI symptoms. Our FMM findings complement (Georgiades, et al., 2013), in which a two-factor, three-class FMM model fitted the ADI-R data. The lower number of classes compared to the current study may be due to the sample used, as Georgiades et al's (2013) sample was younger (4-years-old) and all were diagnosed with ASD, whereas the current study also included unaffected co-twins and those with broader spectrum diagnoses.

As predicted, the FMM model specified a two-factor solution to the ADI-R items; one factor corresponding to social/communication deficits and a second factor corresponding to RRBIs. This two-factor solution suggests that social-communication symptoms and RRBIs are distinct symptom dimensions in ASD. Frazier, et al. (2012) also obtained two separable, but highly correlated, social-communication and RRBIs factors, suggesting that these two dimensions are not necessarily independent of each other.

The FMM model also suggests that social and communication impairments are not distinct symptom dimensions, corresponding with the recent DSM-5 changes from a three-symptom structure in the DSM-IV to a two-dimensional symptom structure for ASD: social-communication deficits and fixated interests and repetitive behaviours (American Psychiatric Association, 2000, 2013). The current results also support Snow, Lecavalier, and Houts' (2009) findings that the ADI-R contained two factors corresponding to a social-communication factor and an RRBI factor, using both CFA and exploratory factor analysis. However, Duku et al. (2013) found that a two-factor model did not extend to comparisons of the two symptom dimensions between ASD subgroups that differed in terms of age, sex, or verbal ability. Instead, both Duku, et al. (2013) and Liu et al. (2011) found that a six-factor model was the most adequate explanation of the autism symptom phenotype.

The current study FMM model specified a five-class solution to the symptom heterogeneity present in the participants. When examining the symptom profile of these classes, the results largely suggest that the five classes are defined by symptom severity, incrementally increasing from Class 1 through to Class 5. Class 1 had the lowest social and communication impairments, with few RRBIs, and mainly comprised unaffected co-twins. Class 2 had slightly more social and communication impairments than Class 1, but few RRBIs (comparable to Class 1). The severity of social and communication impairments significantly increased through Class 3 to Class 5, with individuals assigned to Class 5 showing the most severe social and communication impairments. Likewise, RRBIs significantly increased through Class 3 to 5, with individuals assigned to Class 5 showing the most restricted and repetitive behaviours, although there was more class overlap in RRBIs than in social-communication symptoms, perhaps due in part to lower numbers of items addressing the former than the latter in ADI-R.

Previous research has investigated the subgrouping of individuals within ASD using latent class analysis. For example, Frazier, et al. (2012) study reported just two classes, which could be distinguished as an ASD class versus a non-ASD class. Based on these findings, Frazier, et al. (2012) posited a categorical approach to ASD. The current study and previous empirical findings do not support a categorical distinction in ASD. Beuker et al. (2013) investigated ASD symptoms in a large sample of 11,332 mothers of 18-month-old infants. The LCA indicated four classes, with a distinction between social and communication symptoms, and stereotypies and rigidities. The classes were defined by (1) high symptom scores, (2) subclinical symptoms of ASD, (3) high RRBI scores, but low social-communication symptoms, and (4) low symptom scores across all domains. Comparable to the current study and that by Georgiades, et al. (2013), the classes were largely defined by symptom severity.

The second aim of this chapter was to explore the similarities and differences between individuals assigned to each subgroup in terms of age, gender, diagnosis, current experimenter-rated ASD symptomatology (on ADOS), cognition and co-occurring behavioural emotional, and sensory abnormalities. These analyses suggested that Class 1 contained an equal gender split with mostly unaffected individuals (non-diagnosed co-twins) with low ASD symptoms and low comorbid symptoms and few sensory abnormalities. Class 2 was similar to Class 1 in having an equal gender split, similar IQ, equally low RRBI scores and few sensory abnormalities, but contained more broad-spectrum diagnoses, more social-communication symptoms and more

behavioural problems than Class 1. Class 3 comprised three-quarter males, a third with a broad-spectrum diagnosis and two-thirds with ASD. Class 3 had a similar IQ to Class 1, 2, and 4, with moderate ASD symptoms and sensory abnormalities and more comorbid symptoms than Class 2. Class 4 comprised mostly males with ASD, had a lower IQ than Class 1 and 2, and had more severe ASD impairments and high rates of comorbid symptoms and sensory abnormalities. Class 5 comprised three-quarter males, all with ASD diagnoses, severe ASD symptoms and a lower IQ than other classes, over half had abnormal rates of behavioural difficulties (as defined by the SDQ) with high rates of comorbid symptoms, and presented with high rates of sensory abnormalities.

It appears that increased ASD symptoms may increase risk for concurrent behavioural symptoms. Lundstrom et al. (2011) found that even relatively mild autistic-like behaviours increased the risk for comorbid symptoms. In addition, Hallett et al. (2013) investigated anxiety and ASD within the SR sample and found that individuals with ASD and broader spectrum diagnoses had higher levels of anxiety than typically-developing individuals. Furthermore, some anxiety subscales were correlated with increased social and communicative impairments. This corresponds to Classes 4 and 5 who had higher anxiety and higher levels of social and communicative impairments compared to Classes 1 and 2.

In addition, Class 5 had high rates of sensitivity across tactile, taste/smell and visual/auditory domains and high rates of sensation seeking and auditory filtering. Class 5's sensory profile was very similar to the 'taste/smell sensitive' sensory group that Lane, Molloy, and Bishop (2014) indicated in a clustering-based study to identify sensory subgroups within ASD using the SSP. In contrast, Class 4 showed much lower rates in these domains, but had high rates of movement sensitivity and so their profile could reflect the 'generalized sensory difference' subgroup that Lane, et al. (2014) identified.

8.4.2 Limitations

Some limitations warrant consideration. Firstly, males were overrepresented in certain classes. Secondly, a typically-developing control group was not used in the present analyses as controls in SR study did not complete diagnostic assessments. Another limitation concerns statistical power; multiple comparisons were made across classes. This was taken into consideration with significance thresholds set at a stricter level. Furthermore, there was a large amount of missing

data in Class 5 as half of the group were nonverbal individuals with ASD. This meant that these individuals were unable to complete many of the cognitive tasks and so produced a considerable amount of missing data within this group. This small sample size within Class 5 could mean that there was lack of statistical power to detect significant differences. Also of note is the IQ assessment for the nonverbal individuals with ASD. Although a nonverbal test of IQ was used, floor effects made it difficult to establish a reliable IQ score. Consequently these individuals were given an IQ score of 49, perhaps skewing Class 5's average IQ score. On the other hand, an IQ score of 49 (one less than the lowest possible score on the WASI) may in fact be an overestimate of functioning for some of these individuals.

A further limitation regards the questionnaire measures used within the study. Using questionnaires to measure behavioural symptoms has its own disadvantages, such as measurement error, rater bias, and item inclusion/exclusion. Within this study, the questionnaire measures used have been validated in typically developing samples, but not all have good psychometric information from the ASD population. Additionally, both parent and child reports of behavioural symptoms were used. Modest rater agreements on behavioural symptoms were observed, yet differing results were found when comparing classes when using parent or child report measures.

There are further limitations in using the FMM approach, such as bias in choosing the best fitting model, which can lead to misspecification of the number of classes or misspecification of the factor structure. Additionally, FMM does not permit the investigation of different factor structures within different classes. It instead forces a common factor structure in each class. In the current study, a two factor structure was imposed in each class. It could be hypothesised that the factor structure differs across classes, but it is not possible to investigate this hypothesis using the FMM approach. Furthermore, fewer RRBI items were available from the ADI-R in the factor structure than social-communication symptoms. This means that some RRBI symptoms may not have been fully covered, which may have biased the outcome of the FMM.

8.4.3 Future Directions

The current study used only ASD symptoms to examine subgroups within ASD. However, the subgroups established within this study differed in their level of comorbid symptoms, with many showing abnormal levels of symptoms in other psychiatric disorders, such as anxiety,

hyperactivity, and conduct problems. Even though ASD is conceptualised as a single disorder, a large amount of heterogeneity within ASD may in fact be due to the frequently associated features and comorbid symptoms. Therefore, it may be beneficial to explore whether there are subgroups within ASD who have distinct comorbid symptom profiles, such as in van der Meer, et al. (2012) study in which ASD [+ADHD] and ADHD [+ASD] subgroups were found. This could involve an approach that includes social-communicative and RRBI items, plus items relating to comorbidities within the factor mixture model.

Wardenaar and de Jonge (2013) proposed that for homogeneous diagnoses to occur, the three levels of heterogeneity (person, symptom, and time) need to be modelled. The current study used FMM to model person-level and symptom-level heterogeneity. To cover all three sources of variation, a statistical technique that also includes repeated symptom measures across time should be implemented according to Wardenaar and de Jonge (2013). For example, latent growth curve analysis could be used (Muthén, Asparouhov, & Rebollo, 2006). It could then be explored whether the classes identified in this study follow a different developmental trajectory.

A quantitative genetic approach could be used to investigate genetic predispositions for the different ASD classes/subgroups. Also, Lundstrom, et al. (2011) study suggested that there are both common genetic and environmental predispositions between autistic-like traits and comorbid disorders. It would also be interesting to investigate whether common genetic and environmental predispositions can elucidate the co-occurrence of ASD symptomatology and concurrent behavioural problems within this sample.

8.4.4 Conclusion

In sum, a ‘two-factor, five-class’ FMM was chosen as showing the best fit to the present data; one factor corresponding to social-communication impairments, and a second factor corresponding to restricted and repetitive behaviours and interests. According to the final FMM, individuals could be classified into five relatively homogeneous subgroups. These five subgroups were largely based on severity of ASD symptoms. Across the subgroups, individuals received different diagnoses, had a differing IQ profile, and a differing symptom profile. In addition, subgroups with more severe ASD symptoms also had increased severity of concurrent behavioural symptoms and sensory abnormalities. This suggests that assessments for concurrent behavioural symptoms and sensory abnormalities should be conducted alongside

diagnostic assessments for ASD. Future work should endeavour to examine the developmental trajectories of potential subgroups in ASD and attempt to validate the categorisation using genetic, neurophysiological and cognitive biomarkers.

Chapter 9 General Discussion

The primary aim of this thesis has been to explore the possible fractionation of ASD at the cognitive level. The following sections will serve to re-examine the research questions posed in this thesis and to summarise the main findings. General interpretations will be considered using the framework of the fractionated triad theory of ASD. The limitations of the current work and potential future research will then be considered.

9.1 Summary of Results

9.1.1 How Prevalent are Cognitive Deficits in ASD?

To establish whether a multiple cognitive deficit model is a viable explanation of ASD, the prevalence of multiple cognitive deficits/differences in ASD should first be examined. Consequently, Chapter 4 investigated the prevalence of multiple cognitive atypicalities in adolescents with ASD, their unaffected co-twins and a control group. This approach was taken in Chapter 4 as there are many mixed findings in the literature regarding cognitive deficits in ASD, with data typically reported for just one area of cognition because of the predominance of single cognitive deficit accounts of ASD.

Taking a group mean difference approach, it was reported in Chapter 4 that the ASD group performed significantly worse than the control group across individual cognitive tasks measuring CC, EF and ToM, except for tasks measuring local processing ability (EFT and Block Design Task). This finding was confirmed in Chapter 5; the ASD group performed significantly worse on the derived factors purported to measure EF, ToM and global processing than both the unaffected co-twin group and control group, but no differences were found for the local processing factor.

However, due to the heterogeneity in cognitive performance within the ASD group, it was decided that means may not fully reflect performance across groups and so analyses reported in Chapter 4 examined how many individuals showed no cognitive atypicalities, a single cognitive atypicality, dual cognitive atypicalities, or multiple cognitive atypicalities. Overall, it was found that the ASD group had atypical performance on more cognitive tasks than either comparison group. Furthermore, nearly a third of adolescents with ASD had multiple cognitive atypicalities, i.e., they had atypical performance in tasks across the cognitive domains of CC, EF and ToM. This proportion was significantly higher than that in the unaffected co-twin (11%) and

control (6%) groups. However, multiple cognitive atypicalities were not exhibited by every individual with ASD, as might be predicted from a strong version of a multiple deficit account. Instead, multiple cognitive atypicalities seem to be characteristic, but not a universal feature, of ASD.

The findings in Chapter 4 are supported by the results of Pellicano (2010a) and Vanegas and Davidson (2015). Both Pellicano (2010a) and Vanegas and Davidson (2015) investigated multiple cognitive deficits in ASD in a younger age range to the SR sample (7-11 years), with Pellicano (2010a) additionally using a longitudinal design. At a group level, both Pellicano (2010a) and Vanegas and Davidson (2015) also demonstrated that children with ASD had deficits across cognitive domains, which persisted over time, supporting our claim that there are multiple cognitive deficits in ASD. However, Pellicano (2010a) examined individual cognitive profiles, and found that multiple cognitive deficits were not universal in ASD and the cognitive deficits became less marked through mid- to late-childhood. However, it should be considered that in both Chapter 4 and in Pellicano (2010a) study, a somewhat arbitrary definition of a cognitive atypicality was used. In fact, when Pellicano (2010a) used a more lenient definition of atypicality, all of the children with ASD had multiple cognitive atypicalities. Therefore, there are challenges in defining what constitutes 'atypical performance' on cognitive tasks. Furthermore, both studies used a categorical approach to performance by defining whether individuals had typical or atypical performance in cognitive tasks. Instead, future work might usefully take a continuous approach to a/typical cognitive performance.

Due to the prevalence of cognitive atypicalities in ASD, it could be suggested that the three main cognitive domains of CC, EF, and ToM that have been the focus of this thesis, may potentially be cognitive endophenotypes of ASD. Chapter 7 used a twin-modelling approach to investigate the heritability of these cognitive atypicalities, and examined the genetic and environmental overlap between these cognitive atypicalities and ASD. Using the cognitive factors derived in Chapter 5, it was found that global processing, executive function and theory of mind were modestly associated with ASD phenotypically. Local processing showed strong genetic influence. However, all other cognitive domains showed low genetic influence and substantial non-shared environmental influences. Overall, there was limited support for the proposal that cognitive atypicalities are viable endophenotypes of ASD. These results do not fit family studies of the broader autism phenotype that have suggested an intermediate cognitive

profile (to include deficits in CC, EF and ToM) in relatives, and which have used these findings to propose that these cognitive atypicalities may be part of the endophenotype of ASD (cf. Nyden, et al., 2011). Chapter 7 was the first study to investigate cognitive endophenotypes using a twin modelling approach. The results support Nyden, et al. (2011), who found that weak CC and ToM are not part of the endophenotype of ASD. However, Nyden, et al. (2011) did find evidence of deficits in planning ability in the relatives of those with an ASD, suggesting that this may be a cognitive endophenotype of ASD. This was not supported in Chapter 7, where the executive function factor showed low genetic influence.

In addition to investigating the prevalence of cognitive atypicalities specifically in individuals with a diagnosis of ASD, it was possible to explore aspects of the broader autism phenotype in this thesis since the unaffected co-twins of twins with ASD may be expected to share some (subclinical) traits or cognitive characteristics. Overall, Chapter 4 reported a mixed pattern of results regarding whether the unaffected co-twins of those with ASD shared cognitive features with their affected siblings. It appeared that the unaffected co-twin group had an intermediary cognitive profile, with cognitive performance not as poor as those with ASD, nor as good as the control group. In addition, a higher proportion of the unaffected co-twins had multiple cognitive atypicalities as compared to the control group. However, taking the cognitive factor scores derived in Chapter 5, the unaffected co-twins had significantly higher scores than the ASD group across the EF, ToM and global processing factors, with no significant differences in cognitive factor scores when compared to the control group.

9.1.2 Are Cognitive Deficits Distinct in ASD?

The focus of Chapter 5 was to examine if the cognitive functions relevant to ASD are distinct and independent from one another. A factor analytical approach was used to investigate the underlying structure of a cognitive task battery to create data-driven cognitive factors. It was found that the cognitive battery could be reduced to four factors; two factors relating most closely to the concept of CC, one factor relating to ToM, and one factor relating mostly to EF. A comparison of the factor structure in the ASD group compared to the control group indicated that the factor structure differed between groups. However, the confirmatory factor analyses performed in Chapter 6 in the ASD group only supported the underlying factor structure specified in the exploratory factor analysis.

The relationship between the four factors was also investigated in Chapter 5 and it was found that in the ASD group; (1) ToM and EF factors were correlated, and (2) ToM and global processing factors were correlated. No significant relationships between factors were found in either of the comparison groups. Therefore, the hypothesis that cognitive features are independent was supported within unaffected co-twin and control groups only. This suggests that these cognitive features are distinct by adolescence in typical development. However, cognitive features may remain (or become) inter-related in ASD. This may be due to developmental cascades in ASD, i.e., an abnormal cognitive function may impact a separate cognitive function over development. For example, impaired executive functions may influence the (poor) development of theory of mind (found to be related in Chapter 5). To examine developmental cascades, longitudinal data are required, and so it was not possible to test this hypothesis using the current dataset. However, it will be important to examine in future work the cognitive risk factors that may lead to cascades of events influencing the development of the cognitive and behavioural features of ASD. Targeted interventions could then interrupt these cascades improving outcomes for individuals with ASD.

9.1.3 What is the Link Between Cognitive Deficits and the Symptoms of ASD?

In Chapter 4, correlation analyses within the ASD group indicated that the number of cognitive tasks that an individual displayed atypical performance in was related to the severity of their ASD symptoms. There was also a significant difference in the severity of ASD symptoms according to the number of cognitive domains in which an individual showed atypicality (none, single, dual, and multiple). In addition, those with ASD who were affected by multiple cognitive atypicalities also had more severe ASD symptoms compared to those with no cognitive atypicalities. This indicates that underlying cognitive phenotypes may increase the likelihood or severity of ASD impairments. The results of Chapter 4 also support Happé, Ronald, et al. (2006) proposal that we need to move away from single cognitive accounts of ASD as multiple cognitive deficits may provide a better explanation of the behavioural symptoms of the disorder.

In Chapter 8, behavioural subtypes of ASD were distinguished, with more severe ASD symptoms characterising Classes 4 and 5. In addition, lower cognitive factor scores were found for Classes 4 and 5 in the EF factor, Class 4 in the ToM factor, and Classes 3 and 4 in the global processing factor, as compared to Class 1 (lowest ASD symptoms).

Chapter 6 specifically investigated the link between cognitive deficits and the symptoms of ASD based on the prediction from the fractionated triad account that specific cognitive deficits will relate differentially to specific symptom domains in ASD. Using the ADOS as a measure of current symptom severity in ASD revealed that ToM was related to the social symptoms and EF was related to communication and RRBI symptoms of ASD. Using the ADI-R as a measure of past and current symptom severity in ASD, it was revealed that local processing was related to communication and social symptoms, and EF was related to communication symptoms in this ASD sample. Therefore the only consistent finding was a link between executive function and communication symptoms in ASD.

Joseph and Tager-Flusberg (2004) also used an individual differences approach to examine the link between cognition and ASD symptomatology. A link was found between ToM and planning abilities (EF) and ADOS communication symptoms, independent of language ability. However, there were no relationships between cognition and social symptoms or RRBIs once language was accounted for. The findings of Chapter 6 did not control for language ability as Joseph and Tager-Flusberg (2004) did, but did control for IQ. Furthermore, Joseph and Tager-Flusberg (2004) study contained 30 participants with ASD, in contrast to a sample five times that size in the SR study. This means that Chapter 6 could use more complex analyses to extend Joseph and Tager-Flusberg (2004) analyses, with more power to detect significant associations. Therefore, the results of Chapter 6 provide empirical support for the hypothesis that ToM deficits underlie current and observable social symptoms of ASD and support Joseph and Tager-Flusberg (2004) finding that EF may underlie communication symptoms.

9.1.4 Is It Possible to Identify More Homogeneous Subtypes of ASD?

One of the most challenging aspects of this thesis was the substantial heterogeneity among cognitive and behavioural features in ASD. Therefore, the main aim of Chapter 8 was to identify homogeneous subgroups within ASD using a novel approach called factor mixture modelling. This method assigned individuals to one of five relatively homogeneous subgroups based on their social-communication and RRBI symptoms, supporting the work of Georgiades, et al. (2013). The severity of ASD symptoms incrementally increased through the subgroups. Expanding on the work of Georgiades, et al. (2013), those in subgroups with more severe ASD symptoms also had more concurrent behavioural symptoms, such as depression, anxiety, behavioural issues and sensory abnormalities. It therefore appears that increased ASD

symptoms may increase risk for concurrent behavioural symptoms. This suggests that assessments for concurrent behavioural symptoms and sensory abnormalities should be conducted alongside diagnostic assessments for ASD. It could also be hypothesised that individuals in different subgroups may have a differential response to treatment. However, the subgroups identified in Chapter 8 still had a wide variation in their symptom and concurrent behavioural profiles, which was also the case with Georgiades, et al. (2013) subgroups. The approach taken in Chapter 8 did confirm significant heterogeneity in the symptom and comorbid profiles of those with ASD by adolescence. In addition, studies should consider alternatives to grouping participants as ASD vs. non-ASD to overcome the obstacle of heterogeneity. Overall, reducing heterogeneity using these approaches to inform groups could be an important implication and a next step for future research, such as using cognitive level phenotypes (as discussed in Section 9.3).

9.1.5 How Do the Results Inform the Fractionation of ASD at the Cognitive Level?

The novel findings in this thesis help clarify our understanding of ASD at the cognitive level. The main theme of this thesis was to investigate the fractionated triad approach to ASD that was proposed by Happé and Ronald (2008). Chapter 2 extended Happé and Ronald (2008) original review by examining the literature that specifically related to the fractionation of ASD at the cognitive level. From the review in Chapter 2, it was determined that very few studies have considered multiple cognitive deficits as characterising ASD as suggested by the fractionated account of ASD, and also how these deficits may link to the behavioural symptoms of ASD.

The findings in this thesis do not support a strong version of the fractionated account of ASD, in which distinct causes at the genetic and neural levels relate to distinct deficits at the cognitive level, and these are associated with distinct symptoms of ASD at the behavioural level (as described in Chapter 1). There were some selective relationships between cognitive deficits and the behavioural symptoms of ASD, but these differed depending on the diagnostic symptom measure used. The results from the ADOS model presented in Chapter 6 suggested that distinct cognitive features uniquely influence the current behavioural symptoms of ASD. However, the ADI model presented a different pattern of results that somewhat challenge the predictions of the fractionated theory of ASD, as distinct cognitive domains did not relate to specific behavioural symptoms. Therefore, a weaker version of the fractionated theory is supported in which multiple cognitive deficits characterise ASD, and these cognitive deficits

relate to distinct symptoms, as in the strong version, but a single cognitive deficit can explain more than one symptom domain, and more than one cognitive deficit can explain a single symptom domain.

The hypothesis that was tested in Chapter 6 and the one suggested by the fractionable triad account postulates a *direct* effect between cognition and behaviour. However, the fractionable triad account does not consider *indirect* effects in the link between a cognitive domain and a symptom domain, such as the role of mediating factors, a combination of factors, such as multiple cognitive domains together, or *bidirectional* effects between cognition and behaviour, which could also be important. As previously discussed in Chapter 2, the link between cognition and behaviour is interposed by compensatory skills. The current thesis accounted for IQ in analyses. Some of the additional compensatory skills that could be considered are verbal ability, working memory, attention and environmental aspects such as amount of social contact.

Additionally, heterogeneity needs to be considered within the fractionated account of ASD. The fractionated theory model proposes that there is an interaction between multiple deficits at the cognitive level that influence symptomatology at the behavioural level in ASD. There are also likely to be multiple pathways from the cognitive to the behavioural level due to the heterogeneity inherent in ASD. There is also the possibility that a single cognitive model, even one that considers multiple cognitive deficits within its framework, may not be sufficient to explain the link between cognition and behaviour in ASD. For example, there may be different cognitive subtypes with differing behavioural profiles. Overall, the results of the thesis do strongly suggest the need to move away from single cognitive deficit models of ASD, which have recently become popular again with the implication that ASD is caused by a failure of Bayesian inference (e.g., Pellicano & Burr, 2012), and consider that multiple cognitive deficit models can provide a better explanation of ASD.

One of the remaining challenges is how to test the fractionated account of ASD. For example, Ronald, Happé, and Plomin (2005) used twin modelling analyses to provide evidence of the fractionation of ASD at the behavioural level. Chapter 8 also suggested that social-communication symptoms and RRBIs are distinct symptom dimensions in ASD. The challenge is how to extend this to the cognitive level.

9.2 Limitations

Limitations that were specific to the design or the analyses of each study are presented at the end of each chapter. Discussion here will focus on limitations that were more general or reoccurring throughout the thesis.

TEDS is a large longitudinal twin study with a representative sample of the UK population. In addition, the SR study is the largest population-derived study of children with twins with ASD carried out to date. Despite these strengths, there are also limitations to consider, such as the low level of selective attrition from TEDS, particularly those with low IQ.

In addition, there were not enough females within the SR sample to look at sex-specific models. To add, the selection procedure started with a population-based sample but still relied on ASD diagnosis and diagnostic assessments, which may be sex-biased. Therefore, the final SR sample may not be representative of the female ASD population.

One of the limitations of the SR study is the cognitive tasks used to assess each cognitive domain. The relative sensitivity of each cognitive task is currently unknown and the tasks were unmatched for discriminative power and reliability. In addition, there is no norm data available for these cognitive tasks, with undetermined psychometric properties and test-retest reliability. Therefore, it is not known whether these tasks are of equivalent difficulty. It should be noted that this is a pervasive challenge in cognitive research.

In addition, the cognitive tasks may not fully encompass the cognitive domains that the tasks are purported to measure. For example, theory of mind may comprise of not just social-cognitive reasoning (e.g., false-belief reasoning), but also social-perceptual skills utilising both explicit and implicit judgements (Yang, Rosenblau, Keifer, & Pelphrey, 2015).

Finally, the thesis investigated the cognitive endophenotype of ASD. However, this could only be based on the broader autism phenotype as expressed in siblings as there was no parent data available. Instead, Szatmari, Zwaigenbaum, and Bryson (2004) have suggested that the broader autism phenotype may be more ‘dilute’ in siblings than in parents.

9.3 Directions for Future Research

Some future research directions that were related to each study were proposed at the end of each chapter. Some additional research directions are proposed in this section after considering the whole thesis.

Chapter 8 used factor mixture modelling (FMM) to identify more homogenous subgroups within ASD based on the behavioural symptoms of ASD in an attempt to distinguish 'apples from oranges'. This approach could be expanded to include more than just the ASD symptoms characterised by the ADI-R items (conceivably just the 'apples'). It would be insightful to conduct FMMs to encompass ASD symptoms (ADI-R and ADOS), IQ, cognitive atypicalities, comorbid symptoms and sensory abnormalities. This may reveal not only the 'apples' (ranging from small to large as in Chapter 8), but indeed sort the apples from the oranges to provide subtypes of ASD that will be informative both clinically and for research.

In addition, Chapter 8 investigated behavioural subgroups within ASD. This design could be expanded to explore if there are cognitive subgroups within ASD. Chapter 4 found that cognitive atypicalities are highly prevalent in ASD. Using latent class analysis, it may be possible to identify more homogenous cognitive subgroups in typical development and ASD based on cognitive task performance. Preliminary analyses using the SR sample has identified four cognitive subgroups in ASD: (1) atypicalities across cognitive factors (17%); (2) poor CC, EF and ToM (68%); (3) weak CC (6%); and (4) no cognitive atypicalities (9%). Subgroup 1 and 2 also had more severe ASD symptoms (Brunsdon et al. accepted conference abstract, 2015). The next step will be whether these subgroups have differing profiles.

The families from the SR Study are currently involved in an 18-year-old follow-up study. Furthermore, the twins from the SR study are part of the TEDS, a longitudinal population-based study, and so data exists at various time points throughout the twins' development. This provides the potential to conduct longitudinal analyses, building on Pellicano (2013) analyses. Analyses, such as latent growth modelling, could potentially be used to explore cognitive functioning across development and its altering relations with ASD symptoms. These analyses could help test the multiple cognitive deficit model of ASD and the fractionated triad theory of ASD.

One potential longitudinal research question that could be answered by the TEDS dataset is whether earlier social and non-social symptoms of ASD differentially predict later cognitive atypicalities. In Chapter 4, we found that nearly one third of the ASD group presented with multiple cognitive atypicalities, and many had single or dual cognitive atypicalities. As these results are based on TEDS twins, it is possible to investigate the earlier developmental trajectory of those with multiple cognitive deficits in adolescence. It could be hypothesised that those with multiple cognitive atypicalities will follow different developmental trajectories to those without cognitive atypicalities. This approach could potentially identify those at risk of developing multiple cognitive impairments.

Furthermore, this thesis investigated the fractionated triad in a clinically diagnosed sample. It is also possible to explore the predictions proposed in Chapter 2 in the general population as ASD represents quantitative extremes of traits that are normally distributed in the general population. Using data from TEDS, it is possible to investigate if there is fractionation of social and non-social cognitive abilities in the general population with the hypothesis that social and non-social cognitive abilities will be relatively independent from each other. It is also possible to investigate if social and non-social cognitive abilities relate differentially to autistic-like traits (social, communication, and non-social symptoms), as indicated by the CAST using bivariate and multivariate genetic modelling.

In addition to expanding on the analyses presented in this thesis, new lines of research would also be beneficial. The SR study was conducted in adolescence and one of the main criticisms of the approach is that of the suitability of the cognitive tasks for this age range. In addition, the fractionated theory should be investigated at earlier developmental time points. Therefore, an experimental study utilising an age-appropriate cognitive task battery at younger time points in both typical development and children with ASD may be fruitful in informing a multiple cognitive account of ASD. In addition, previous research has not gained information about everyday cognitive abilities, which could be assessed using parental questionnaires. This may provide a more comprehensive account of cognition in both typical development and in ASD. For example, Vanegas and Davidson (2015) found that everyday executive functioning problems were more severe than perseverative issues on a card-sort task. The approach could investigate individual differences in performance across cognitive measures to examine their relationship to the symptoms of ASD, which would add to the findings of Chapter 6. It is

important to investigate this at younger time points to understand how the relationship between cognition and behaviour may alter throughout development.

In addition to an experimental approach, it may also be informative to take a neuroimaging approach, such as using electroencephalography (EEG) and event-related potentials (ERPs), to understand the associations between cognitive traits. EEG may be useful to measure the areas of brain activity associated with different cognitive atypicalities and to examine if there is overlap between areas of brain activity for cognitive features, therefore using a brain-based approach to examine if cognitive features are distinct.

It was previously discussed that there may be possible cognitive subgroups within ASD. If cognitive subgroups were identified, then it may be beneficial to investigate the developmental trajectories of these cognitive subgroups within ASD and their interactions throughout developmental with the behavioural symptoms. A useful tool to investigate this proposal would be growth mixture modelling and would require cognitive testing at multiple time points. The identification of distinct cognitive trajectories in ASD would provide support for the fractionated account.

Chapter 6 investigated the relationship between cognitive features of ASD and symptomatology. However, the association was only assessed in one direction and causation cannot be implied from the results. One way to examine causality is through intervention studies. For example, children with and without ASD could then be given cognitive training, such as ToM training. Chapter 6 found a link between ToM and social symptoms and so following intervention, it would be predicted that social symptoms would improve. A causal mechanism could then be implied to inform treatment approaches.

9.4 Concluding Remarks

The main focus of this thesis was to explore the potential for a multiple cognitive model of ASD using the predictions of the fractionated triad account. One of the strengths of the thesis was its attempt to utilise more complex statistical techniques to investigate the cognitive atypicalities within ASD. The findings highlight the prevalence of multiple cognitive deficits/differences in adolescents with ASD. A weaker version of the fractionated theory was supported, in which multiple cognitive deficits characterise ASD, and these cognitive deficits relate to distinct symptoms of ASD. One of the most challenging aspects of this thesis was the substantial

heterogeneity among cognitive and behavioural features of ASD. Studies should consider alternatives to grouping participants as ASD vs. non-ASD to overcome the obstacle of heterogeneity. Additionally, this heterogeneity needs to be considered within the fractionated triad account of ASD. Overall, the results of the thesis do strongly suggest the need to move away from single cognitive deficit models of ASD and consider that multiple cognitive deficit models can provide a better explanation of ASD.

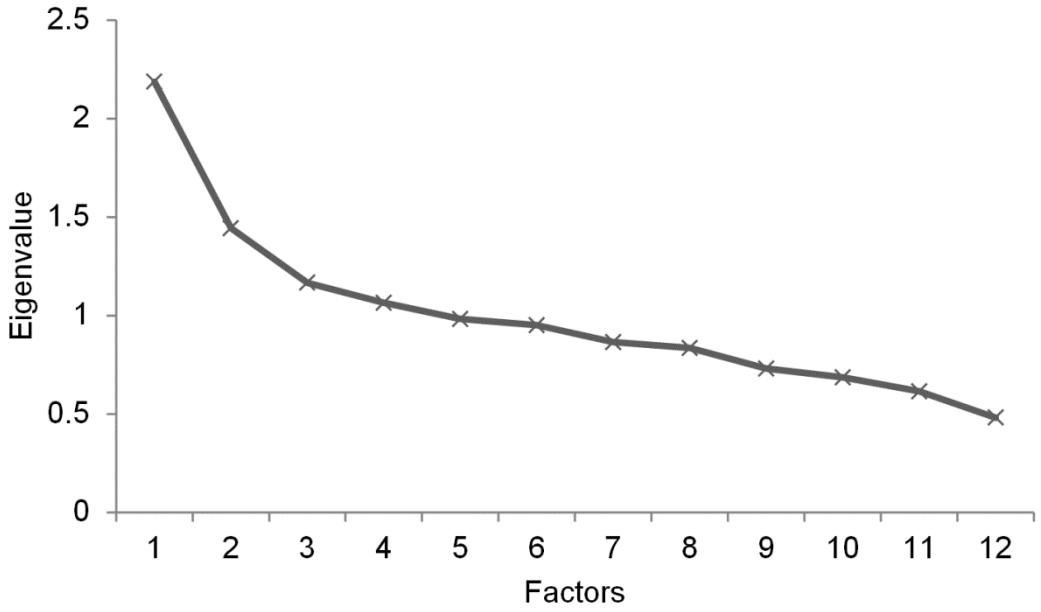
Appendices

Appendix 1. A list of measures used in the SR Study (Chapter 3).

Diagnostic Measures	
Questionnaire	Child Autism Spectrum Test (CAST)
Telephone Interview	Development and Wellbeing Assessment (DAWBA)
Parent Interview	Autism Diagnostic Interview-Revised (ADI-R)
Child Observation	Autism Diagnostic Observation Schedule (ADOS)
Clinician	Best-Estimate Consensus Diagnosis
Questionnaire Measures	
Behaviour Problems	Strengths and Difficulties Questionnaire (SDQ)
Anxiety	Revised Child Anxiety and Depression Scale (RCADS)
Depression	Mood and Feelings Questionnaire (MFQ)
Health	Questions about twins' past and present health
Alexithymia	Toronto Alexithymia Scale (TAS-20)
Sensory Behaviours	Short Sensory Profile (SSP), Adolescent/Adult Sensory Profile
Medical History	Questions about family's medical history
Talent	Questions about twins' special abilities and talents

Cognitive Assessments	
IQ	Wechsler Abbreviated Scale of Intelligence (WASI), Raven's Coloured Progressive Matrices, British Picture Vocabulary Scales-Revised (BPVS)
Baseline Tasks	Reaction Time, Inspection Time, How I Feel Questionnaire
Language	Clinical Evaluation of Language Fundamentals-2 (CELF-2) subtests, Nonsense Word Repetition
Central Coherence	Embedded Figures Task, Fragmented Pictures, Homographs Reading Test, Planning Drawing Task - Part A, Sentence Completion Task
Executive Function	Letter Fluency (FAS), Intra-/Extra-dimensional Task, Luria Hand Game, Planning Drawing Task - Part B
Social Cognition	Penny Hiding Game, Triangles Animation Task, False-Belief Stories, Ekman's Emotional Faces Task, Speech Expression
Parent Interviews	
Pregnancy and Birth	Obstetric Enquiry Schedule (OES)
Medical History	Family History Interview (FHI)

Appendix 2. Eigenvalues for principal axis factoring (Chapter 5)



Appendix 3. Example of bivariate twin analysis model to estimate causes of variation (ACE) for joint analyses of ordinal and continuous data (Chapter 7)

```
## ------------------------------------------------------------------------------------------------------------------------
## Bivariate model fitting
##Executive Functioning = cognitive factor (EF), continuous
##ASD = consensus diagnosis (CD), ordinal - three category, 2 thresholds = 0,1,2
## ------------------------------------------------------------------------------------------------------------------------

### Run a model with 2 thresholds for CD

maxth       <- 2                                    # max number of thresholds
TH1         <- 1.64                                 # prevalence 5%, fix, Broad Spectrum
TH2         <- 2.33                                 # prevalence 1%, fix, Autism

nv          <- 2                                    # number of variables per twin
ntv         <- nv*2                                 # number of variables per pair

# change CD to be mxfactors with 2 thresholds
CogCD[,c(3,4)]  <- mxFactor(CogCD[,c(3,4)], c(0 : 2))

names (CogCD); describe(CogCD)                      # names and descriptives of variables
selVars     <- c('EF1', 'CD1', 'EF2', 'CD2')        # select EF and CD for twin 1 and 2
Vars        <- c('EF','CD')                         # select variables
mzData      <- subset(CogCD, zyg==1, selVars)       # select MZ twin data
dzData      <- subset(CogCD, zyg==2, selVars)       # select DZ twin data

# (1) Specify Bivariate Correlation Model: Executive Functioning (Cognitive Factor, continuous) - Consensus Diagnosis (Selection Variable, ordinal)
# ------------------------------------------------------------------------------------------------------------------------

# Expected means for EF, fixed for CD
Mean        <- mxMatrix(type="Full", nrow=1, ncol=ntv, free=c(T,F,T,F), labels=c("meanEF", NA, "meanEF", NA), values=c(-1,0,-1,0), name="ExpMean")

# Expected thresholds
Thres       <-mxMatrix(type="Full", nrow=maxth, ncol=nv, free=F, values=c(TH1,TH2,TH1,TH2),  name="Expthres" )
```

```
# Standard deviations, fixed at 1 for EF
SD          <-mxMatrix( type="Diag", nrow=ntv, ncol=ntv, free=c(T,F,T,F),
            values=c(1,1,1,1), labels=c("sdCD", "sdEF", "sdCD", "sdEF"), lbound=0,
            name="sd" )

# MZ correlation matrix with starting values
# Rph = phenotypic correlation, RefMZ = EF correlation between twins
# xtrxtwMZ = cross-twin, cross-trait correlation, RcdMZ = CD correlation between twins
MZCor       <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=c(T,T,T,T,T,T), values=c(-
            .3,.2,-.2,-.2,.9,-.3), labels=c("Rph", "RefMZ", "xtrxtwMZ", "xtrxtwMZ", "RcdMZ",
            "Rph"), lbound=-.999, ubound=.999, name="Rmz"  )

# MZ covariance matrix
MZCov       <- mxAlgebra( expression=sd %&% Rmz, name="ExpCovMZ" )

# DZ correlation and covariance matrices with starting values
DZCor       <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=c(T,T,T,T,T,T), values=c(-
            .3,.1,-.1,-.1,.45,-.3), labels=c("Rph", "RefDZ", "xtrxtwDZ", "xtrxtwDZ", "RcdDZ",
            "Rph"), lbound=-.999, ubound=.999, name="Rdz"  )
DZCov       <- mxAlgebra( expression=sd %&% Rdz, name="ExpCovDZ" )


# Data objects
DataMZ      <- mxData(observed=mzData, type="raw")      #MZ data to use
DataDZ      <- mxData(observed=dzData, type="raw")      #DZ data to use

# Objective objects for Multiple Groups
objmz       <- mxFIMLObjective( covariance="ExpCovMZ", means="ExpMean",
            dimnames=selVars, thresholds="Expthres", threshnames=c("CD1","CD2"))
objdz       <- mxFIMLObjective ( covariance="ExpCovDZ", means="ExpMean",
            dimnames=selVars, thresholds="Expthres", threshnames=c("CD1","CD2"))

# Combine Groups
modelMZ     <- mxModel(Mean, Thres, MZCor, SD, MZCov, DataMZ, objmz, name="MZ" )
modelDZ     <- mxModel(Mean, Thres, DZCor, SD, DZCov, DataDZ, objdz, name="DZ" )
minus2ll    <- mxAlgebra( expression=MZ.objective + DZ.objective, name="m2LL" )
obj         <- mxAlgebraObjective("m2LL" )

# Confidence intervals for MZ & DZ correlations
Conf1       <- mxCI (c  ('MZ.Rmz[1,2]', 'MZ.Rmz[1,3]', 'MZ.Rmz[2,3]', 'MZ.Rmz[2,4]' )  )
Conf2       <- mxCI (c  ('DZ.Rdz[1,3]', 'DZ.Rdz[2,3]', 'DZ.Rdz[2,4]' )  )
```

```
# Correlation model
CorModel        <- mxModel( "Cor", modelMZ, modelDZ, minus2ll, obj, Conf1, Conf2)

# RUN Correlation MODEL
CorFit          <- mxRun(CorModel, intervals=T)
(CorSumm        <- summary(CorFit))                     #Means & descriptives for model
round(CorFit@output$estimate,4)

# (2) Specify Constrained Bivariate ACE Model using Cholesky Decomposition
# # ------------------------------------------------------------------------------------------------------------------------

# Matrix for expected Means and thresholds
Mean            <- mxMatrix(type="Full", nrow=1, ncol=ntv, free=c(T,F,T,F), labels=c("meanEF",
                NA, "meanEF", NA), values=c(-.35,0,-.35,0), name="ExpMean")
Thres           <- mxMatrix(type="Full", nrow=maxth, ncol=nv, free=F,
                values=c(TH1,TH2,TH1,TH2), name="Expthres" )

# Matrices to store a, c, and e Path Coefficients
pathA           <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=c(.1,-.5,.9),
                labels=c("a11", "a21", "a22"), name="a" )
pathC           <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=c(.01,-
                .01,.01),  labels=c("c11", "c21", "c22"), name="c" )
pathE           <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=c(.9,-.05,.3),
                labels=c("e11", "e21", "e22"), name="e" )

# Matrices generated to hold A, C, and E computed Variance Components
covA            <- mxAlgebra( expression=a %*% t(a), name="A" )
covC            <- mxAlgebra( expression=c %*% t(c), name="C" )
covE            <- mxAlgebra( expression=e %*% t(e), name="E" )

# Algebra to compute standardised variance components
covP            <- mxAlgebra( expression=A+C+E, name="V" )
StA             <- mxAlgebra( expression=A/V, name="h2")
StC             <- mxAlgebra( expression=C/V, name="c2")
StE             <- mxAlgebra( expression=E/V, name="e2")

# Algebra to compute Phenotypic, A, C & E correlations
matI            <- mxMatrix( type="Iden", nrow=nv, ncol=nv, name="I")
rph             <- mxAlgebra( expression= solve(sqrt(I*V)) %*% V %*% solve(sqrt(I*V)),
                name="Rph")
rA              <- mxAlgebra( expression= solve(sqrt(I*A)) %*% A %*% solve(sqrt(I*A)),
                name="Ra" )
```

```
rC          <- mxAlgebra( expression= solve(sqrt(I*C)) %*% C %*% solve(sqrt(I*C)),
               name="Rc" )
rE          <- mxAlgebra( expression= solve(sqrt(I*E)) %*% E %*% solve(sqrt(I*E)),
               name="Re" )

# Algebras to put Standardised Parameter Estimates in a Matrix with col and row labels
rowVars     <- rep('Vars',nv)
colVars     <- rep(c('h2','c2','e2'),each=nv)
estVars     <- mxAlgebra( expression=cbind(h2,c2,e2), name="Est", dimnames =
               list(rowVars,colVars))

# Algebra to compute Rph-A, Rph-C & Rph-E for Cont and ASD
rph21       <- mxAlgebra( expression = cbind ( (sqrt (h2[1,1])*Ra [2,1]*sqrt (h2[2,2])),  (sqrt
               (c2[1,1])*Rc  [2,1]*sqrt  (c2[2,2])),  (sqrt  (e2[1,1])*Re[2,1]*sqrt(e2[2,2]))  ),
               name="Rph21" )

# Algebra for expected Variance/Covariance Matrices in MZ & DZ twins
covMZ       <- mxAlgebra( expression= rbind( cbind(A+C+E , A+C),
                          cbind(A+C  , A+C+E))  , name="expCovMZ" )
covDZ       <- mxAlgebra( expression= rbind( cbind(A+C+E      , 0.5%x%A+C),
                          cbind(0.5%x%A+C , A+C+E)), name="expCovDZ" )

# Constrain total variance of Consensus Diagnosis (cd) to unity
con1        <- mxConstraint( expression= V[2,2]==1, name="C1" )

# Data objects for Multiple Groups
dataMZ      <- mxData( observed=mzData, type="raw" )
dataDZ      <- mxData( observed=dzData, type="raw" )

# Objective objects for Multiple Groups
objmz       <- mxFIMLObjective( covariance="expCovMZ", means="ExpMean", dimnames
               = selVars, thresholds="Expthres", threshnames=c("CD1","CD2") )
objdz       <- mxFIMLObjective( covariance="expCovDZ", means="ExpMean", dimnames
               = selVars, thresholds="Expthres", threshnames=c("CD1","CD2") )

# Combine Groups
pars        <- list( Mean, Thres, pathA, pathC, pathE, covA, covC, covE, covP, StA, StC,
               StE, matI, rph, rA, rC, rE, estVars, rph21 )
modelMZ     <- mxModel( pars, covMZ, dataMZ, objmz, name="MZ" )
modelDZ     <- mxModel( pars, covDZ, dataDZ, objdz, name="DZ" )
minus2ll    <- mxAlgebra( expression=MZ.objective + DZ.objective, name="m2LL" )
obj         <- mxAlgebraObjective( "m2LL" )
```

```
Conf1       <- mxCI (c ('h2[1,1]', 'h2[2,2]', 'c2[1,1]', 'c2[2,2]', 'e2[1,1]', 'e2[2,2]') )
Conf2       <- mxCI (c ('Rph[2,1]', 'Ra[2,1]', 'Rc[2,1]', 'Re[2,1]' ) )
Conf3       <- mxCI (c ('Rph21[1,1]', 'Rph21[1,2]', 'Rph21[1,3]') )
AceModel    <- mxModel( "ACE", pars, modelMZ, modelDZ, minus2ll, obj, con1, Conf1,
               Conf2, Conf3)

# ------------------------------------------------------------------------------
# RUN Constrained Bivariate ACE Model

AceFit      <- mxRun(AceModel, intervals=T)
(AceSumm    <- summary(AceFit))                    #Means & descriptives for model
round(AceFit@output$estimate,4)
round(AceFit$Est@result,4)
```

Appendix 4. Series of multinomial logistic regressions to compare classes on age, gender, IQ, ASD symptoms, concurrent behavioural symptoms, sensory abnormalities and cognition (Chapter 8)

Group		Age		Gender		ASD diagnosis		VIQ		PIQ		IQ	
Comparison		b	p	b	p	b	p	b	p	b	p	b	p
1	2	-.04	.129	0.48	.236	**2.34**	**<.001**	.006	.608	.007	.497	.008	.525
1	3	.02	.423	**1.76**	**<.001**	**5.14**	**<.001**	-.02	.146	-.004	.636	-.01	.286
1	4	-.004	.852	**3.58**	**<.001**	**23.38**	**<.001**	**-.03**	**.008**	-.008	.269	-.02	.038
1	5	-.03	.284	**1.71**	**.001**	**23.38**	**<.001**	**-.04**	**<.001**	**-.03**	**<.001**	**-.03**	**<.001**
2	1	.04	.129	-0.48	.236	**-2.34**	**<.001**	-.006	.608	-.007	.497	-.008	.525
2	3	.06	.031	**1.28**	**.007**	**2.80**	**<.001**	-.02	.063	-.01	.293	-.02	.115
2	4	.04	.154	**3.11**	**<.001**	**21.04**	**<.001**	**-.03**	**.003**	-.01	.123	-.03	.016
2	5	.009	.769	1.23	.018	**21.04**	**<.001**	**-.05**	**<.001**	**-.03**	**.001**	**-.04**	**<.001**
3	1	-.02	.423	**-1.76**	**<.001**	**-5.14**	**<.001**	.02	.146	.004	.636	.01	.286
3	2	-.06	.031	**-1.28**	**.007**	**-2.80**	**<.001**	.02	.063	.01	.293	.02	.115
3	4	-.02	.308	**1.82**	**.009**	**18.24**	**<.001**	-.01	.195	-.004	.559	-.008	.239
3	5	-.05	.093	-0.06	.921	**18.24**	**<.001**	**-.03**	**.001**	**-.02**	**<.001**	**-.02**	**<.001**
4	1	.004	.852	**-3.59**	**<.001**	**-24.38**	**<.001**	**.03**	**.008**	.008	.269	.02	.038
4	2	-.04	.154	**-3.11**	**<.001**	**-22.04**	**<.001**	**.03**	**.003**	.01	.123	.03	.016
4	3	.02	.308	**-1.82**	**.009**	**-19.24**	**<.001**	.01	.195	.004	.559	.008	.239
4	5	-.03	.335	**-1.88**	**.010**	**43.40**	**<.001**	**-.02**	**<.001**	**-.02**	**<.001**	**-.02**	**<.001**
5	1	.03	.284	**-1.71**	**.001**	**-24.38**	**<.001**	**.04**	**<.001**	**.03**	**<.001**	**.03**	**<.001**
5	2	-.009	.769	-1.23	.018	**-22.04**	**<.001**	**.05**	**<.001**	**.03**	**.001**	**.04**	**<.001**
5	3	.05	.093	0.06	.921	**-19.24**	**<.001**	**.03**	**.001**	**.02**	**<.001**	**.02**	**<.001**
5	4	.03	.335	**1.88**	**.010**	**-43.40**	**<.001**	**.02**	**<.001**	**.02**	**<.001**	**.02**	**<.001**

Group Comparison		Local Processing		Global Processing		Executive Functioning		Theory of Mind		Alexithymia (TAS total)		Alexithymia dx	
		b	p	b	p	b	p	b	p	b	p	b	p
1	2	-.08	.725	-.20	.272	-.17	.299	.26	.289	-.0004	.983	.18	.517
1	3	-.19	.378	**-.51**	**.005**	-.32	.058	-.15	.389	.007	.724	.14	.631
1	4	-.14	.463	**-.48**	**.003**	**-.46**	**.003**	**-.48**	**.002**	.03	.159	.47	.069
1	5	-.25	.407	-.43	.056	-.46	.036	-.41	.054	-.03	.378	-.32	.471
2	1	.08	.725	.20	.272	.17	.299	-.26	.289	.0004	.983	-.18	.517
2	3	-.12	.620	-.31	.091	-.14	.410	-.42	.089	.008	.727	-.05	.880
2	4	-.07	.754	-.28	.093	-.28	.073	**-.74**	**.001**	.03	.186	.29	.306
2	5	-.17	.583	-.22	.322	-.29	.200	**-.67**	**.010**	-.03	.401	-.51	.271
3	1	.19	.378	**.51**	**.005**	.32	.058	.15	.389	-.007	.724	-.14	.631
3	2	.12	.620	.31	.091	.14	.410	.42	.089	-.008	.727	.05	.880
3	4	.05	.814	.03	.835	-.14	.368	-.32	.026	.019	.352	.33	.239
3	5	-.05	.863	.09	.690	-.14	.516	-.25	.222	-.03	.281	-.46	.319
4	1	.14	.463	**.48**	**.003**	**.46**	**.003**	**.48**	**.002**	-.03	.159	-.47	.069
4	2	.07	.754	.28	.093	.28	.073	**.74**	**.001**	-.03	.186	-.29	.306
4	3	-.05	.814	-.03	.835	.14	.368	.32	.026	-.02	.352	-.33	.239
4	5	-.10	.724	.06	.789	-.006	.977	.07	.694	-.05	.082	-.79	.075
5	1	.25	.507	.43	.056	.46	.036	.41	.054	.03	.378	.32	.471
5	2	.17	.583	.22	.322	.29	.200	**.67**	**.010**	.03	.401	.51	.271
5	3	.05	.863	-.09	.690	.14	.516	.25	.222	.03	.281	.46	.319
5	4	.10	.724	-.06	.789	.006	.977	-.07	.694	.05	.082	.79	.075

Group Comparison		ADOS total		ADOS Social		ADOS Communication		ADOS RRBIs		SC Factor		RRBI Factor	
		b	p	b	p	b	p	b	p	b	p	b	p
1	2	**.21**	**<.001**	**0.61**	**.007**	**.30**	**<.001**	0.44	.019	**6.58**	**<.001**	0.85	.135
1	3	**.28**	**<.001**	**0.96**	**<.001**	**.41**	**<.001**	0.45	.016	**11.85**	**<.001**	**3.91**	**<.001**
1	4	**.41**	**<.001**	**1.26**	**<.001**	**.60**	**<.001**	**0.75**	**<.001**	**18.00**	**<.001**	**4.64**	**<.001**
1	5	**.57**	**<.001**	**1.81**	**<.001**	**.83**	**<.001**	**1.16**	**<.001**	**31.53**	**<.001**	**6.32**	**<.001**
2	1	**-.21**	**<.001**	**-0.61**	**.007**	**-.30**	**<.001**	-0.44	.019	**-6.58**	**<.001**	-0.85	.135
2	3	.07	.141	0.35	.040	.11	.108	0.01	.920	**5.27**	**<.001**	**3.06**	**<.001**
2	4	**.20**	**<.001**	**0.65**	**<.001**	**.30**	**<.001**	0.32	.011	**11.42**	**<.001**	**3.80**	**<.001**
2	5	**.36**	**<.001**	**1.20**	**<.001**	**.54**	**<.001**	**0.72**	**<.001**	**24.93**	**<.001**	**5.47**	**<.001**
3	1	**-.28**	**<.001**	**-0.96**	**<.001**	**-.41**	**<.001**	-0.45	.016	**-11.84**	**<.001**	**-3.91**	**<.001**
3	2	-.07	.141	-0.35	.040	-.11	.108	-0.01	.920	**5.27**	**<.001**	**-3.06**	**<.001**
3	4	**.13**	**.001**	0.29	.023	**.19**	**.001**	0.30	.015	**6.15**	**<.001**	**0.74**	**.008**
3	5	**.30**	**<.001**	**0.84**	**<.001**	**.43**	**<.001**	**0.71**	**<.001**	**19.68**	**<.001**	**2.41**	**<.001**
4	1	**-.41**	**<.001**	**-1.25**	**<.001**	**-.60**	**<.001**	**-0.75**	**<.001**	**-18.00**	**<.001**	**-4.65**	**<.001**
4	2	**-.20**	**<.001**	**-0.65**	**<.001**	**-.30**	**<.001**	-0.32	.011	**-11.41**	**<.001**	**-3.80**	**<.001**
4	3	**-.13**	**.001**	-0.29	.023	**-.19**	**.001**	-0.30	.015	**-6.15**	**<.001**	**-0.74**	**.008**
4	5	**.17**	**<.001**	**0.55**	**<.001**	**.24**	**<.001**	**0.40**	**<.001**	**13.52**	**<.001**	**1.67**	**<.001**
5	1	**-.57**	**<.001**	**-1.81**	**<.001**	**-.84**	**<.001**	**-1.15**	**<.001**	**-31.53**	**<.001**	**-6.32**	**<.001**
5	2	**-.36**	**<.001**	**-1.20**	**<.001**	**-.54**	**<.001**	**-0.72**	**<.001**	**-24.94**	**<.001**	**-5.47**	**<.001**
5	3	**-.30**	**<.001**	**-0.84**	**<.001**	**-.43**	**<.001**	**-0.71**	**<.001**	**-19.68**	**<.001**	**-2.41**	**<.001**
5	4	**-.17**	**<.001**	**-0.55**	**<.001**	**-.24**	**<.001**	**-0.40**	**<.001**	**13.52**	**<.001**	**-1.67**	**<.001**

Group Comparison		SDQ Total		SDQ Emotional Symptoms		SDQ Conduct Problems		SDQ Hyperactivity		SDQ Peer Problems		SDQ Prosocial	
		b	p	b	p	b	p	b	p	b	p	b	p
1	2	.01	.760	.04	.709	.03	.823	.009	.932	.03	.823	.03	.823
1	3	.11	.011	.22	.055	.20	.172	.14	.169	.20	.172	.20	.172
1	4	**.14**	**.001**	.17	.095	.25	.053	.22	.017	.25	.053	.25	.053
1	5	.12	.050	.26	.110	.10	.654	.05	.757	.10	.654	.10	.654
2	1	-.01	.760	-.04	.709	-.03	.823	-.009	.932	-.03	.823	-.03	.823
2	3	.10	.033	.16	.144	.16	.283	.13	.226	.16	.283	.16	.283
2	4	**.13**	**.003**	.13	.245	.22	.117	.21	.033	.22	.117	.22	.117
2	5	.11	.087	.22	.195	.06	.776	.04	.806	.06	.776	.06	.776
3	1	-.11	.011	-.22	.055	-.20	.172	-.14	.169	-.20	.172	-.20	.172
3	2	-.10	.033	-.18	.144	-.16	.283	-.13	.226	-.16	.283	-.16	.283
3	4	.03	.492	-.05	.637	.05	.677	.08	.409	.05	.677	.05	.677
3	5	.01	.863	.04	.806	-.10	.643	-.09	.550	-.10	.643	-.10	.643
4	1	**-.14**	**.001**	-.17	.095	-.25	.053	-.22	.017	-.25	.053	-.25	.053
4	2	**-.13**	**.003**	-.13	.245	-.22	.117	-.21	.033	-.22	.117	-.22	.117
4	3	-.03	.492	.05	.637	-.05	.677	-.08	.409	-.05	.677	-.05	.677
4	5	-.02	.779	.09	.565	-.15	.459	-.17	.247	-.15	.459	-.15	.459
5	1	-.12	.050	-.26	.110	-.10	.654	-.05	.757	-.10	.654	-.10	.654
5	2	-.11	.087	-.22	.195	-.06	.776	-.04	.806	-.06	.776	-.06	.776
5	3	-.01	.863	-.04	.806	.10	.643	.09	.550	.10	.643	.10	.643
5	4	.02	.779	-.09	.565	.15	.459	.17	.247	.15	.459	.15	.459

Group Comparison		SDQ Total (Parent Report)		SDQ Emotional Symptoms (Parent Report)		SDQ Conduct Problems (Parent Report)		SDQ Hyperactivity (Parent Report)		SDQ Peer Problems (Parent Report)		SDQ Prosocial (Parent Report)	
		b	p	b	p	b	p	b	p	b	p	b	p
1	2	**.20**	**.001**	**.57**	**<.001**	**.48**	**.008**	.15	.138	**0.38**	**.009**	-0.32	.025
1	3	**.36**	**<.001**	**.80**	**<.001**	**.61**	**.001**	**.36**	**<.001**	**0.87**	**<.001**	**-0.48**	**.001**
1	4	**.41**	**<.001**	**.75**	**<.001**	**.64**	**<.001**	**.56**	**<.001**	**1.03**	**<.001**	**-0.77**	**<.001**
1	5	**.42**	**<.001**	**.61**	**<.001**	**.58**	**.002**	**.63**	**<.001**	**1.23**	**<.001**	**-1.09**	**<.001**
2	1	**-.20**	**.001**	**-.57**	**<.001**	**-.48**	**.008**	-.15	.138	**-0.38**	**.009**	0.32	.025
2	3	**.17**	**<.001**	.23	.030	.13	.301	.21	.031	**0.49**	**<.001**	-0.16	.181
2	4	**.22**	**<.001**	.18	.057	.16	.140	**.41**	**<.001**	**0.65**	**<.001**	**-0.45**	**<.001**
2	5	**.22**	**<.001**	.04	.752	.11	.449	**.48**	**<.001**	**0.85**	**<.001**	**-0.77**	**<.001**
3	1	**-.36**	**<.001**	**-.80**	**<.001**	**-.61**	**.001**	**-.36**	**<.001**	**-0.87**	**<.001**	**0.48**	**.001**
3	2	**-.17**	**<.001**	-.23	.030	-.13	.301	-.21	.031	**-0.49**	**<.001**	0.16	.181
3	4	.05	.166	-.05	.563	.04	.721	.20	.014	0.16	.100	**-0.29**	**.002**
3	5	.05	.222	-.19	.100	-.02	.864	.27	.012	**0.36**	**.006**	**-0.61**	**<.001**
4	1	**-.41**	**<.001**	**-.75**	**<.001**	**-.64**	**<.001**	**-.56**	**<.001**	**-1.03**	**<.001**	**0.77**	**<.001**
4	2	**-.22**	**<.001**	-.18	.057	-.16	.140	**-.41**	**<.001**	**-0.65**	**<.001**	**0.45**	**<.001**
4	3	-.05	.166	.05	.563	-.04	.721	-.20	.014	-0.16	.100	**0.29**	**.002**
4	5	.007	.864	-.14	.182	-.06	.626	.07	.459	0.20	.086	**-0.32**	**.003**
5	1	**-.42**	**<.001**	**-.61**	**<.001**	**-.58**	**.002**	**-.63**	**<.001**	**-0.23**	**<.001**	**1.09**	**<.001**
5	2	**-.22**	**<.001**	-.04	.752	-.11	.449	**-.48**	**<.001**	**-0.85**	**<.001**	**0.77**	**<.001**
5	3	-.05	.222	.19	.100	.02	.864	-.27	.012	**-0.36**	**.006**	**0.61**	**<.001**
5	4	-.007	.864	.14	.182	.06	.626	-.07	.459	-0.20	.086	**0.32**	**.003**

Group Comparison		RCADS Total (Self Report)		RCADS Total (Parent Report)		MFQ (Self Report)		MFQ (Parent Report)		SSP Total		Tactile Sensitivity	
		b	p	b	p	b	p	b	p	b	p	b	p
1	2	.01	.417	.04	.062	-.006	.939	.20	.051	.04	.026	.21	.026
1	3	.03	.048	**.06**	**.008**	.09	.160	**.34**	**<.001**	**.07**	**<.001**	**.34**	**<.001**
1	4	.03	.048	**.07**	**.001**	.11	.062	**.36**	**<.001**	**.10**	**<.001**	**.48**	**<.001**
1	5	.04	.121	**.08**	**.001**	.13	.128	**.32**	**.002**	**.13**	**<.001**	**.63**	**<.001**
2	1	-.01	.417	-.04	.062	.006	.939	-.20	.051	-.04	.026	-.21	.026
2	3	.02	.256	.02	.374	.10	.171	.14	.050	.03	.058	.12	.095
2	4	.02	.295	.03	.104	.12	.077	.16	.017	**.06**	**<.001**	**.26**	**<.001**
2	5	.02	.343	.03	.102	.13	.133	.11	.153	**.09**	**<.001**	**.41**	**<.001**
3	1	-.03	.048	**-.06**	**.008**	-.09	.160	**-.34**	**<.001**	**-.07**	**<.001**	**-.34**	**<.001**
3	2	-.02	.256	-.02	.374	-.10	.171	-.14	.050	-.03	.058	-.12	.095
3	4	-.003	.836	.01	.521	.02	.720	.02	.673	**.03**	**.003**	**.14**	**.011**
3	5	.003	.897	.02	.421	.03	.672	-.03	.663	**.06**	**<.001**	**.29**	**<.001**
4	1	-.03	.048	**-.07**	**.001**	-.11	.062	**-.36**	**<.001**	**-.10**	**<.001**	**-.48**	**<.001**
4	2	-.02	.295	-.03	.104	-.12	.077	-.16	.017	**-.06**	**<.001**	**-.27**	**<.001**
4	3	.003	.836	-.01	.521	-.02	.720	-.02	.673	**-.03**	**.003**	**-.14**	**.011**
4	5	.006	.784	.005	.751	.01	.846	-.05	.415	**.03**	**.010**	**.15**	**.003**
5	1	-.04	.121	**-.08**	**.001**	-.13	.128	**-.32**	**.002**	**-.13**	**<.001**	**-.63**	**<.001**
5	2	-.02	.343	-.03	.102	-.13	.133	-.11	.153	**-.09**	**<.001**	**-.41**	**<.001**
5	3	-.003	.897	-.02	.421	-.03	.672	.03	.663	**-.06**	**<.001**	**-.29**	**<.001**
5	4	-.006	.784	-.005	.751	-.01	.846	.05	.415	**-.03**	**.010**	**-.15**	**.003**

Group Comparison		Taste/Smell Sensitivity		Movement		Under-responsive/ Seeks Sensation		Auditory Filtering		Low Energy/Weak		Visual/Auditory Sensitivity	
		b	p	b	p	b	p	b	p	b	p	b	p
1	2	.11	.112	.07	.614	.03	.637	.09	.161	.13	.040	.11	.380
1	3	.11	.103	.08	.542	**.14**	**.014**	**.25**	**<.001**	.12	.050	**.32**	**.004**
1	4	**.17**	**.005**	**.29**	**.009**	**.25**	**<.001**	**.33**	**<.001**	**.18**	**.002**	**.46**	**<.001**
1	5	**.30**	**<.001**	.265	.039	**.35**	**<.001**	**.36**	**<.001**	**.18**	**.003**	**.62**	**<.001**
2	1	-.11	.112	-.07	.614	-.03	.637	-.09	.161	-.13	.040	-.11	.380
2	3	.003	.959	.01	.917	.11	.056	**.16**	**.004**	-.005	.923	.21	.041
2	4	.06	.232	.22	.040	**.22**	**<.001**	**.25**	**<.001**	.05	.184	**.35**	**<.001**
2	5	**.19**	**.002**	.20	.118	**.32**	**<.001**	**.27**	**<.001**	.06	.195	**.51**	**<.001**
3	1	-.11	.103	-.08	.542	**-.14**	**.014**	**-.25**	**<.001**	-.12	.050	**-.32**	**.004**
3	2	-.003		-.01	.917	-.11	.056	**-.16**	**.004**	.005	.923	-.21	.041
3	4	.06	.259	.21	.051	**.11**	**.013**	.09	.037	.06	.159	.14	.034
3	5	**.19**	**.002**	.18	.143	**.21**	**<.001**	.11	.029	.06	.171	**.30**	**<.001**
4	1	**-.17**	**.005**	**-.29**	**.009**	**-.25**	**<.001**	**-.33**	**<.001**	**-.18**	**.002**	**-.46**	**<.001**
4	2	-.06	.232	-.22	.040	**-.22**	**<.001**	**-.25**	**<.001**	-.05	.184	**-.35**	**<.001**
4	3	-.06	.259	-.21	.051	**-.11**	**.013**	-.09	.037	-.06	.159	-.14	.034
4	5	**.13**	**.010**	-.03	.776	**.10**	**.011**	.03	.541	.008	.827	**.16**	**.004**
5	1	**-.30**	**<.001**	-.27	.039	**-.35**	**<.001**	**-.36**	**<.001**	**-.18**	**.003**	**-.16**	**<.001**
5	2	**-.19**	**.002**	-.20	.118	**-.32**	**<.001**	**-.27**	**<.001**	-.06	.195	**-.51**	**<.001**
5	3	**-.19**	**.002**	-.18	.143	**-.21**	**<.001**	-.11	.029	-.06	.171	**-.30**	**<.001**
5	4	**-.13**	**.010**	.03	.776	**-.10**	**.011**	-.03	.541	-.008	.827	**-.16**	**.004**

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